PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]NAT-LANTHANUM

Lanthanum carbonate dihydrate chewable tablets

Chewable tablets, 250 mg, 500 mg, 750 mg, and 1000 mg, oral

Phosphate binder

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RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS, Gastrointestinal	08/2023

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

NAT-LANTHANUM (lanthanum carbonate dihydrate) is indicated as a phosphate binding agent in patients with end stage renal disease on dialysis.

The use of lanthanum carbonate in controlled clinical studies beyond 2 years is limited. The risk versus benefit from administration beyond two years should be carefully considered. (see **WARNINGS AND PRECAUTIONS, Bone**, **CLINICAL PHARMACOLOGY, Pharmacokinetics, Distribution**, and **CLINICAL TRIALS, Bone Safety**)

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (>65 years of age): Of the total number of patients in clinical studies of lanthanum carbonate, 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.

2 CONTRAINDICATIONS

NAT-LANTHANUM (lanthanum carbonate dihydrate) is contraindicated in:

- Patients with bowel obstruction, ileus and fecal impaction
- Patients with hypophosphatemia
- Patients with hypersensitivity to lanthanum carbonate or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see **DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**.

4 DOSAGE AND ADMINISTRATION

4.1 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.

4.2 Recommended Dose and Dosage Adjustment

The recommended initial daily dose of NAT-LANTHANUM (lanthanum carbonate dihydrate) for adults is 750 mg-1500 mg. 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. NAT-LANTHANUM is presented as a chewable tablet, therefore avoiding the need to take additional fluid.

In clinical studies in ESRD patients, lanthanum carbonate doses up to 4500 mg were evaluated. Most patients required a total daily dose between 1500 mg and 3000 mg of lanthanum carbonate to reduce serum phosphorus levels to less than 6.0 mg/dL (1.92 mmol/L). Doses were generally titrated in increments of 750 mg/day.

Health Canada has not authorized an indication for pediatric use. (see **WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics**)

4.4 Administration

Tablets should be chewed completely before swallowing. The tablets may be crushed as an aid to chewing. Intact tablets should not be swallowed. Consider crushing tablets completely for patients with poor dentition.

4.5 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.

5 OVERDOSAGE

The highest daily dose of lanthanum carbonate administered to healthy adult subjects during a Phase I study was 9000 mg/day for 3 days. The symptoms associated with overdose are adverse reactions such as headache, nausea and vomiting. Given the local activity of NAT-LANTHANUM 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 **NON-CLINICAL TOXICOLOGY, Single- and Repeat-Dose Toxicity**)

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Oral	Chewable tablets / 250 mg, 500 mg, 750 mg, and 1000 mg of elemental lanthanum (as lanthanum carbonate dihydrate)	Colloidal silicon dioxide, dextrates (hydrated), hydroxy propyl cellulose, magnesium stearate and talc.

Each chewable tablet is white to off-white, round shaped tablets and debossed on one side with ‘NAT’ and the dosage strength corresponding to the content of the elemental lanthanum.

NAT-LANTHANUM 250 mg chewable tablets are supplied in bottles of 90 tablets.

NAT-LANTHANUM 500 mg chewable tablets are supplied in bottles of 45 tablets.

NAT-LANTHANUM 750 mg chewable tablets are supplied in bottles of 15 tablets.

NAT-LANTHANUM 1000 mg chewable tablets are supplied in bottles of 10 tablets.

7 WARNINGS AND PRECAUTIONS

Bone

Tissue Deposition: Tissue deposition of lanthanum has been shown with lanthanum carbonate in animal and human studies. The use of lanthanum carbonate in controlled clinical studies beyond 2 years is limited. The risk/benefit from longer-term administration should be carefully considered. In bone biopsies of patients treated with lanthanum carbonate for up to 4.5 years, rising levels of lanthanum were noted over time (see **CLINICAL PHARMACOLOGY, Pharmacokinetics, Distribution; WARNINGS AND PRECAUTIONS, Bone, *Long-term effects*; CLINICAL TRIALS, Bone Safety**). 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 NAT-LANTHANUM should be monitored closely.

Long-term Effects: There were no differences in the rates of fracture in patients treated with lanthanum carbonate compared to Standard Therapy[1] for up to 3 years. The duration of treatment exposure and time of observation in the clinical program is too short to conclude that lanthanum carbonate does not adversely affect bone quality or the risk for fracture or mortality beyond 3 years. (see **CLINICAL TRIALS, Bone Safety**)

Carcinogenesis and Mutagenesis

See **NON-CLINICAL TOXICOLOGY, Mutagenicity and Carcinogenicity** sections.

Gastrointestinal

Serious cases of gastrointestinal obstruction, ileus, subileus, gastrointestinal perforation and fecal impaction have been reported in post-marketing follow-up of patients treated with lanthanum carbonate, some requiring surgery or hospitalization. Some of the cases are found to have lanthanum deposition or Product residues in the gastrointestinal tract. Lanthanum deposition in gastroduodenal mucosa is demonstrated endoscopically as whitish lesions of different sizes and shapes pathological features were identified in gastroduodenal mucosa with lanthanum deposition, such as chronic or active inflammation, glandular atrophy, regenerative changes, foveolar hyperplasia, intestinal metaplasia and neoplasia.

Lanthanum is known to cause constipation (see **ADVERSE REACTIONS, Clinical Trial Adverse Reactions**).

Exercise caution in all patients predisposed to gastrointestinal obstruction, ileus, subileus and perforation; for example those with altered gastrointestinal anatomy (e.g., diverticular disease, peritonitis, history of gastrointestinal surgery, gastrointestinal cancer and gastrointestinal ulceration), hypomotility disorders (e.g., constipation, diabetic gastroparesis), and when used with medications known to potentiate these effects. Some cases were reported in patients with no history of gastrointestinal disease.

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[1] 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.

During treatment with NAT-LANTHANUM, physicians and patients should remain vigilant for signs and symptoms of gastrointestinal disorders, especially constipation and abdominal pain/distention which may indicate bowel obstruction, ileus or subileus.

Treatment with NAT-LANTHANUM should be re-evaluated in patients who develop severe constipation or other severe gastrointestinal signs and symptoms.

The safety of lanthanum carbonate in patients with acute peptic ulcer, ulcerative colitis or Crohn's disease has not been established in clinical studies. Caution should be used in patients with these conditions.

Advise patients to chew the tablet completely and not swallow whole (see **DOSAGE AND ADMINISTRATION, Administration**). Serious gastrointestinal complications, such as those described above, have been reported in association with unchewed or incompletely chewed tablets.

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.

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

Renal:

Patients with renal impairment may develop hypocalcaemia. Serum calcium levels should therefore be monitored at regular intervals in this patient population and appropriate supplements should be given.

7.1 Special Populations

7.1.1 Pregnant Women

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. NAT-LANTHANUM is not recommended for use during pregnancy. (see **NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology**)

7.1.2 Breast-feeding

The excretion of lanthanum in milk has not been studied in animals. It is unknown whether lanthanum is excreted in human breast milk. Because many drugs are excreted in human milk precaution should be exercised.

7.1.3 Pediatrics

Pediatrics (<18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of lanthanum carbonate in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for 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 NAT-LANTHANUM in pediatric patients is not recommended. (see **CLINICAL TRIALS, Bone Safety**)

7.1.4 Geriatrics

Of the total number of patients in clinical studies of lanthanum carbonate, 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.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

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

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

In three placebo-controlled studies in end stage renal disease (ESRD) patients, the most common adverse events for lanthanum carbonate were gastrointestinal events such as nausea and vomiting, and they generally abated over time with continued dosing. Adverse events that were more frequent (≥5% difference) in the lanthanum carbonate group are presented in Table 2.

Table 2: Adverse Events that were More Common to Lanthanum carbonate in Placebo-Controlled, Double-blind Studies with Treatment Periods of 4 - 6 Weeks

System Organ Class Preferred Terminology (WHOART)	**Lanthanum carbonate** **n=180** **(%)**	**Placebo** **n = 95** **(%)**
Dialysis Complication-NW		
Dialysis Graft Occlusion	7.8	1.1
Gastrointestinal System Disorders		
Nausea	10.6	5.3
Vomiting	9.4	4.2
Abdominal Pain	5.0	0.0

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

The safety of lanthanum carbonate was studied in two long-term clinical trials that included 1215 patients treated with lanthanum carbonate and 944 with alternative therapy. Sixteen percent (16%) of patients in these comparative, open-label studies discontinued in the lanthanum carbonate-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 (≥5% in either treatment group) in both the long-term (2 year), open-label, active-controlled, study of lanthanum carbonate vs. alternative therapy (Study A) and the 6-month, comparative study of lanthanum carbonate vs. calcium carbonate (Study B) are shown in Table 3 and Table 4, respectively. In Table 4, 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 3: Number of Withdrawals/Phosphate Levels Achieved by Study Phase

	Study A*		**Study B****	
WITHDRAWALS				
	Lanthanum carbonate	**Alternative Therapy**	**Lanthanum carbonate**	**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%)
MEAN SERUM PHOSPHATE LEVEL ACHIEVED				
Titration Phase	6.43 mg/dL* (2.06 mmol/L)	5.71 mg/dL* (1.85 mmol/L)	1.87 mmol/L **	1.66 mmol/L **
Maintenance Phase	6.17 mg/dL (1.97 mmol/L)	6.05 mg/dL (1.94 mmol/L)	1.73 mmol/L	1.72 mmol/L

*Study A: Patients in the lanthanum carbonate group were titrated over a six-week period starting from a dose of 750 mg/day and then maintained on doses up to 3000 mg/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 lanthanum carbonate group were titrated from 375 mg/day up to their optimal dose and then maintained on doses up to 3000 mg/day. The calcium carbonate group started the titration phase at their optimal dose and were maintained on doses up to 9000 mg/day.

Table 4: Incidence of Treatment-Emergent Adverse Events that Occurred in ≥5% of Patients (in Either Treatment Group) and in Both Comparative Studies A and B

	Study A %		**Study B %**	
	Lanthanum carbonate (n=682)	**Alternative* Therapy Adjusted Rates** (n=677)	**Lanthanum carbonate** (n=533)	**Calcium Carbonate** (n=267)
Nausea	37	29	16	13
Vomiting	27	22	18	11
Dialysis graft complication	25	24	3	5

Table 4: Incidence of Treatment-Emergent Adverse Events that Occurred in ≥5% of Patients (in Either Treatment Group) and in Both Comparative Studies A and B				
	Study A %		Study B %	
	Lanthanum carbonate (n=682)	Alternative* Therapy Adjusted Rates (n=677)	Lanthanum carbonate (n=533)	Calcium Carbonate (n=267)
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 lanthanum carbonate 375 mg-3000 mg as elemental lanthanum and calcium carbonate 1500 mg-9000 mg elemental calcium.

8.3 Less Common Clinical Trial Adverse Reactions

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

Blood and Lymphatic System Disorders: Eosinophilia

Ear and Labyrinth Disorders: Vertigo

Endocrine Disorders: Hyperparathyroidism

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

General Disorders and Administration Site Conditions: Asthenia, chest pain, fatigue, malaise, pain, peripheral edema, thirst

Infections and Infestations: Gastroenteritis, laryngitis

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

Metabolism and Nutrition Disorders: Anorexia, appetite increased, hyperglycemia, hyperphosphatemia, hypocalcemia, hypophosphatemia

Musculoskeletal and Connective Tissue Disorders: Arthralgia, myalgia, osteoporosis

Nervous System Disorders: Dizziness, taste alteration

Skin and Subcutaneous Tissue Disorders: Alopecia, erythematous rash, itching, pruritus, sweating increased

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 lanthanum carbonate had a lower incidence of hypercalcemic episodes relative to patients on calcium-based phosphate binder ($p<0.001$).

8.5 Post-Market Adverse Reactions

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

Gastrointestinal disorders: dyspepsia, ileus, intestinal obstruction, intestinal perforation, product residue present, subileus

General disorder: tooth injury

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

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Lanthanum carbonate dihydrate 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.

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

9.3 Drug-Behavioural Interactions

Drug-behavioural interactions have not been established.

9.4 Drug-Drug Interactions

The drugs listed in the table below are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

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

Table 5: Established or Potential Drug-Drug Interactions

Proper/Common name	Source of Evidence	Effect	Clinical comment
Calcitriol (1,25-dihydroxy vitamin D3)	CT	Lanthanum carbonate: 1000 mg three times a day for 1 day Calcitriol: 2 x 0.5 mcg Co-administration in healthy subjects.	Did not significantly alter peak concentrations or overall extent of absorption of calcitriol.
Ciprofloxacin (quinolone antibiotics)	CT	Co-administration of lanthanum carbonate with quinolone antibiotics in a single dose study in healthy volunteers	Lanthanum carbonate should not be taken simultaneously with oral quinolone antibiotics. May reduce the absorption as a result of complex formation. The bioavailability of oral ciprofloxacin was decreased by approximately 50%.
Citrate	CT	Lanthanum carbonate: 1000 mg Co-administration with citrate in healthy subjects.	Lanthanum carbonate absorption and pharmacokinetics were not affected
Digoxin	C	Digoxin: 0.5 mg Lanthanum carbonate: 3 x 1000 mg on the day prior to exposure and one dose of 1000 mg on the day of co-administration in healthy subjects.	No effects of lanthanum were found on the absorption of digoxin. Potential pharmacodynamic interactions between lanthanum and digoxin were not evaluated. None of the drug interaction studies were done with the maximum recommended therapeutic dose of lanthanum carbonate.
Fat soluble vitamins (A, D, E and K), vitamin B12 or other nutrients	CT		Lanthanum appears not to affect the intestinal absorption (see **CLINICAL TRIALS, Open-Label, Active Controlled Studies**)

Table 5: Established or Potential Drug-Drug Interactions

Proper/Common name	Source of Evidence	Effect	Clinical comment
Levothyroxine (Thyroid hormones)	C		NAT-LANTHANUM should not be taken simultaneously with thyroid hormones replacement therapy and closer monitoring of TSH levels is recommended in patients receiving both medicinal products. Bioavailability of levothyroxine was decreased by approximately 40%.
Metoprolol	C	Metoprolol: 100 mg Lanthanum carbonate: 3 x 1000 mg on the day prior to exposure and one dose of 1000 mg on the day of co-administration in health subjects.	No effects of lanthanum were found on the absorption of metoprolol. Potential pharmacodynamic interactions between lanthanum and metoprolol were not evaluated. None of the drug interaction studies were done with the maximum recommended therapeutic dose of lanthanum carbonate.
Warfarin	C	Warfarin: 10 mg Lanthanum carbonate: 3 x 1000 mg on the day prior to exposure and one dose of 1000 mg on the day of co-administration in healthy subjects.	No effects of lanthanum were found on the absorption of warfarin. Potential pharmacodynamic interactions between lanthanum and warfarin (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.
Other Potential Interactions			
Antibiotics (tetracycline, doxycycline)	T	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 NAT-LANTHANUM.

Table 5: Established or Potential Drug-Drug Interactions

Proper/Common name	Source of Evidence	Effect	Clinical comment
Compounds known to interact with antacids (chloroquine, hydroxychloroquine and ketoconazole)	T	Potential for NAT-LANTHANUM to interact with compounds which bind to cationic antacids (e.g., aluminum-, magnesium-, or calcium-based).	It is recommended that compounds known to interact with antacids should not be taken within 2 hours of dosing with NAT-LANTHANUM (e.g., chloroquine, hydroxychloroquine and ketoconazole)

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

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

The drug interactions profile of lanthanum carbonate 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 NAT-LANTHANUM or monitoring blood levels.

9.5 Drug-Food Interactions

The effect of food on the bioavailability of lanthanum carbonate 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. (see **CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption**)

9.6 Drug-Herb Interactions

Interactions of NAT-LANTHANUM with herbs have not been established.

9.7 Drug-Laboratory Test Interactions

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

9.8 Drug-Lifestyle Interactions

Interactions of lanthanum carbonate with lifestyle have not been established.

10 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.

10.1 Mechanism of Action

NAT-LANTHANUM (lanthanum carbonate dihydrate) acts in the lumen of the gut to bind dietary phosphorus released from food during digestion. Lanthanum carbonate dihydrate 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.

10.2 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. NAT-LANTHANUM 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.

10.3 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 dihydrate's efficacy.

Table 6: Summary of Lanthanum Pharmacokinetic Parameters in [specific patient population]

	C_{max}	T_{max}	$t_{½}$ (h)	$AUC_{0-\infty}$	CL	Vd
Single dose mean	1.06 (±1.04) ng/mL		36	31.1 (±40.5) ng·h/mL		

Absorption:
Following single or multiple dose oral administration of lanthanum carbonate 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 mg to 1000 mg 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 1000 mg lanthanum carbonate dihydrate three times daily, the mean (±sd) lanthanum C_{max} was 1.06 (±1.04) ng/mL, and the mean AUC_{last} was 31.1 (±40.5) ng·h/mL. During long-term administration (52 weeks) in renal dialysis patients, the mean lanthanum concentration in plasma was approximately 0.6 ng/mL. Regular blood level monitoring in renal dialysis patients taking lanthanum carbonate dihydrate (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 NAT-LANTHANUM 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 0.90 ng/mL in plasma, and <0.006 to 1.0 mcg/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 lanthanum carbonate 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**). Cases of lanthanum carbonate deposition in gastrointestinal mucosa, mainly after long-term use, have been reported. The clinical significance of this is not yet known.

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 40 mcg/mL does not have relevant inhibitory effects on any of the CYP450 isoenzymes tested (1A2, C9, 2C19, 2D6 and 3A4).

Elimination:
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 lanthanum carbonate 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 2806 mcg/kg (range 530 to 5513 mcg/kg) and the mean concentration was 1903 mcg/kg (range 543 to 5683 mcg/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.

Special Populations and Conditions

Pediatrics: Pharmacokinetics of lanthanum carbonate has not been studied in pediatric patients. (see **WARNINGS AND PREACAUTION, Special Populations**)

11 STORAGE, STABILITY AND DISPOSAL

Store between 15 - 30°C.

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

12 SPECIAL HANDLING INSTRUCTIONS

No special handling instructions are required for this drug product.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

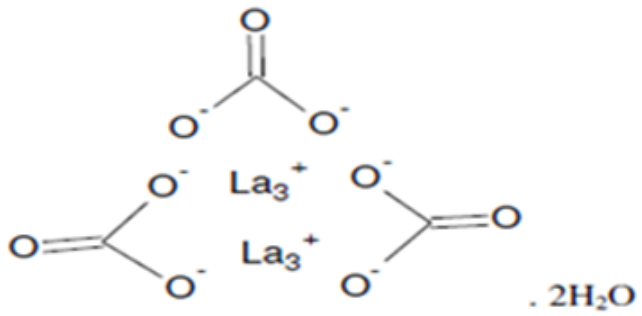
Drug Substance

Proper name: lanthanum carbonate dihydrate

Chemical name: Carbonic acid, lanthanum (III+) salt (3:2) dihydrate

Molecular formula and molecular mass: NAT-LANTHANUM contains lanthanum carbonate (2:3) dihydrate with molecular formula $La_2(CO_3)_3 \bullet 2H_2O$ and a molecular mass of 493.84 g/mol.

Structural formula:



Physicochemical properties: Lanthanum carbonate dihydrate, a white to off white powder, is a basic carbonate consisting primarily of carbonate dihydrate, $La_2(CO_3)_3 \bullet 2H_2O$. A macromolecular structure is formed from the association of water molecules across the crystal lattice. The pKa values for its salt, carbonic acid, are 10.51 and 6.68. Lanthanum carbonate is insoluble in organic solvents and soluble in dilute hydrochloric acid.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

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.

Table 7: Summary of patient demographics for clinical trials in hyperphosphatasemia in end stage renal disease

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
LAM-IV-202	Phase 2, randomized, double-blind, placebo-controlled study with 3 parts (Part 1: 2-week washout; Part 2: 4-week dose titration; Part 3: 4-week randomized treatment)	Daily dose of 250 mg, 375 mg, 750 mg, 1500 mg, or 2250 mg; Chewable tablets taken orally; Duration: 4-week titration period and 4-week double blind period)	Total = 59: Placebo 19; Lanthanum carbonate 36	55 (29 – 79) years	56/44
LAM-IV-204	Phase 2, randomized, double-blind, placebo controlled, parallel group, dose ranging study with 3 parts (Part 1: 1 to 3-week single-blind placebo run-in; Part 2: 6-week double blind treatment; Part 3: 2-week run-out)	Daily dose of 225 mg, 675 mg, 1350 mg, or 2250 mg; Chewable tablets taken orally; Duration: 6 weeks	Total = 144: Placebo 32; 225 mg 27; 675 mg 29 1350 mg 30 2250 mg 26	56 (23 – 84) years	55/44
LAM-IV-301	Phase 3, open-label, comparator controlled study with 5 parts (Part 1: 1 to 3-week washout; Part 2: 5-week dose titration; Part 3: 20-week open label treatment; Part 4: 24-week open label extension; Part 5: 2-year optional extension)	Daily dose of 375 mg, 750 mg, 1500 mg, 2250 mg or 3000 mg; Chewable tablets taken orally; Duration: up to 5 weeks titration + 20 weeks open label treatment + 24 weeks open label extension + 2 years extension	Total = 800: Comparator (Calcium Carbonate) 267; Lanthanum carbonate: 533	59 (19-85) years	66/34

Table 7: Summary of patient demographics for clinical trials in hyperphosphatasemia in end stage renal disease

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
LAM-302	Phase 3, dose titration, randomized, double blind, placebo controlled, parallel group study with 3 parts (Part 1: 1 to 3-week washout; Part 2: 6-week open label dose titration; Part 3: 4-week double blind maintenance treatment	Daily dose of 375 mg, 750 mg, 1500 mg, 2250 mg, or 3000 mg; Chewable tablets taken orally; Duration: 6 weeks titration + 4 weeks of double blind treatment	Total = 93: Placebo 44; Lanthanum carbonate 49	60 (21-83) years	66/34
LAM-307	Phase 3, open-label, randomized, multicenter, comparator controlled parallel group study with 3 parts (Part 1: 1 to 3-week washout; Part 2; 6-week dose titration; Part 3: 24-month maintenance on the randomized treatment)	Daily dose of 375 mg, 750 mg, 1500 mg, 2250 mg, or 3000 mg; Chewable tablets taken orally; Duration: 1-3 weeks washout; 6 weeks dose titration; 24 months maintenance treatment	Total =1359 Lanthanum carbonate: 682 Comparator: 677	55 (10-91) years	59/41

14.2 Study Results

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.

Fifty-four subjects [37 (33%) patients on lanthanum carbonate and 17 (53%) patients on placebo] withdrew from the study after randomization. The reasons for discontinuation are described in Table 8 below.

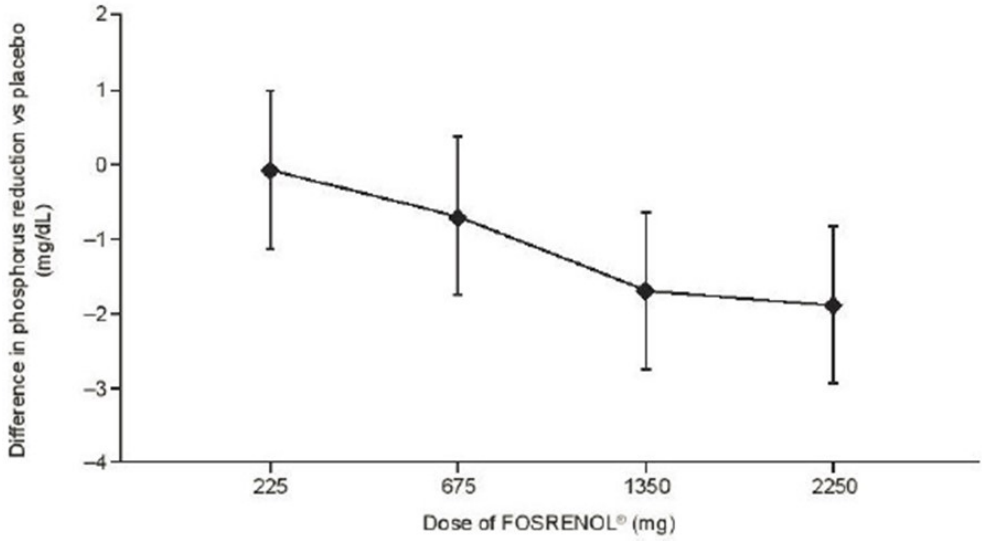
Table 8: Reasons for Discontinuation in Study LAM-204

Reason for Discontinuation	Lanthanum carbonate (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 mg/dL, PO_4XCa >80 mg^2/dL^2, and change in PTH >500 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 Lanthanum carbonate 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 5.6 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.

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 1.9 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 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 lanthanum carbonate 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 lanthanum carbonate only. The purpose of the extension was primarily to assess safety and long-term tolerability of lanthanum carbonate.

Of the 767 subjects who entered the titration period (ITT population), 101 [lanthanum carbonate: 60 (11.8%); Calcium: 41 (16.0%)] withdrew before entering the maintenance phase of the study. Two-hundred and ninety-one subjects [lanthanum carbonate: 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 9.

Table 9: Reasons for Discontinuation in Study LAM-301

Reason for Discontinuation	Lanthanum carbonate (n=533 randomized)	Calcium (n=267 randomized)
Total withdrawn	271 (50.8%)	154 (57.7%)
Death	19 (3.6%)	11 (4.1%)
Adverse events	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 1.73 mmol/L (representing -0.74 mmol/L from baseline) in the lanthanum carbonate group (doses up to 3000 mg/day), and 1.73 mmol/L (representing -0.75 mmol/L from baseline in the Calcium group (doses up to 9000 mg/day) in patients who completed the maintenance period.

In Study LAM-307, 1359 patients were randomized to receive either lanthanum carbonate or Standard Therapy[2]. 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 lanthanum carbonate therapy, and 677 were randomized to Standard Therapy[2].

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 lanthanum carbonate group and 356 (52.6%) were in the Standard Therapy[2] group.

The reasons for discontinuation are shown in Table 10.

Table 10: Reasons for Discontinuation in Study LAM-307

Reason for Discontinuation	Lanthanum carbonate (n=682 randomized)	Standard Therapy[a] (n=677 randomized)
Total withdrawn	487 (71.3%)	356 (52.6%)
Death[b]	42 (6.2%)	96 (14.2%)
Adverse event	98 (14.4%)	29 (4.3%)
Exceeded pre-specified safety criteria:		
Two PO_4 >10 mg/dL	32 (4.7%)	22 (3.3%)
Two PO_4 <2.0 mg/dL	0	2 (0.3%)
Two $CaXPO_4$ >90 mg^2/dL^2	14 (2.1%)	7 (1.0%)
Calcium >11.5 mg/dL	2 (0.3%)	1 (0.1%)
Increase PTH >500 pg/mL	5 (0.7%)	1 (0.1%)
Protocol violation	13 (1.9%)	5 (0.7%)
Withdrew consent	107 (15.7%)	34 (5.0%)
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%)

a. 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.

b. Represents End of Study entry as the investigator-determined reason for study withdrawal. There were patients who died after study termination (13 lanthanum carbonate; 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 of Study LAM-301, taking lanthanum carbonate only, to a total of three years. Maintenance of phosphate reduction was observed in patients treated with lanthanum carbonate for up to 3 years of which 62% received daily doses of either 2250 mg or 3000 mg at Week 58. There were minimal dose changes throughout the remainder of the study. Of the 90 patients who completed the third year of therapy, 49 (54.4%) had a phosphate level better than the target of 1.8 mmol/L.

[2] 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.

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, maintenance of reduction in serum phosphate level was observed. There was no evidence of adverse safety concerns after long-term lanthanum carbonate treatment in any body system, including the hepatic system, bone and central nervous system in the small number of patients remaining in their sixth year of treatment.

No effects of lanthanum carbonate on serum levels of 25-hydroxy and 1,25-dihydroxy vitamin D, 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 lanthanum carbonate 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[3] group was observed from averaged data, the median rising 3-fold from a baseline of 53 mcg/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 mcg/kg (range 122-5513 mcg/kg). Median and range concentrations at 18 and 24 months were similar to 12 months. The median at 54 months was 4246 mcg/kg (range 1673-9792 mcg/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 lanthanum carbonate (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 (lanthanum carbonate: n=31, Standard Therapy[3]: n=32), and 52 patients had biopsies at baseline and 2 years (lanthanum carbonate: n=31, Standard Therapy[3]: 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.

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[3] 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.

14.3 Comparative Bioavailability Studies

Pharmacodynamic Equivalence Study

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, and therefore, the use of a conventional comparative bioavailability approach to demonstrate lanthanum bioequivalence between two products would be meaningless. Furthermore, due to low bioavailability of lanthanum (less than 0.002%), an alternative assessment method is required.

An in vivo study using pharmacodynamic endpoints in healthy subjects was used to replace the conventional human pharmacokinetic in vivo studies in assessing the equivalence of NAT-LANTHANUM (lanthanum carbonate chewable tablets) versus FOSRENOL® (lanthanum carbonate chewable tablets from Shire Pharma Canada ULC). The primary endpoint used for pharmacodynamic equivalence assessment was the average daily urinary phosphate excretion over three days.

A randomized, double blind, balanced, two-treatment, two-period, two-sequence, multiple dose, two-way crossover study comparing daily urinary excretion of phosphorus for three days with tid administration of a 1000 mg tablet dose of NAT-LANTHANUM chewable tablets versus FOSRENOL® (lanthanum carbonate) chewable tablets was conducted in healthy adult male volunteers under fed conditions. The difference between formulations in average daily urinary phosphate excretion (LS means and 90% CI) was estimated and compared for the determination of pharmacodynamic equivalence.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: In vitro studies have shown that lanthanum binds phosphate in the physiologically relevant pH range of 3 to 7. In normal rats, lanthanum carbonate (1000 mg/kg p.o.) increased fecal excretion of co-administered [^{32}P]-phosphate and decreased urinary [^{32}P]-phosphate excretion compared to vehicle-treated controls, indicative of effective dietary phosphate binding. In partially nephrectomised rats, lanthanum carbonate treatment (≥1000 mg/kg) reduced, but not significantly, the hyperphosphataemia and hyperparathyroidism associated with chronic renal failure.

The absolute oral bioavailability of lanthanum (from lanthanum carbonate) was estimated from oral and intravenous studies in rats to be 0.0007%. 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. In bile-duct cannulated rats, biliary excretion of intravenous lanthanum (administered as the soluble lanthanum chloride) was the predominant route of elimination.

Long-term studies in animals have shown deposition of lanthanum in tissues, mainly the gastrointestinal tract, mesenteric lymph nodes, liver and bone (see also **CLINICAL PHARMACOLOGY, Pharmacokinetics, Distribution**). There is no evidence from animal studies that lanthanum crosses the blood brain barrier.

Single- and Repeat-Dose Toxicity

In single-dose oral toxicity studies in mice and rats, lanthanum carbonate at doses up to 2000 mg/kg resulted in no deaths and produced no overt signs of toxicity. Single-dose intravenous toxicity studies in mice and rats were conducted using the soluble chloride salt of lanthanum to ensure delivery of high systemic lanthanum doses. The maximum non-lethal intravenous doses were 3.0 mg/kg in the mouse and 6.25 mg/kg in the rat. In both species, at 6.25 mg/kg, histopathological changes in the liver included degeneration and necrosis of hepatocytes, with hemorrhage and inflammation 2 days post-dose.

In repeat-dose oral toxicity studies in mice (for up to 99 weeks), rats (for up to 104 weeks), and dogs (for up to 52 weeks), lanthanum carbonate was well tolerated at the maximum practicable doses of 1500 mg/kg/day in rodents and 2000 mg/kg/day in dogs. In a 13-week oral toxicity study in mice, lanthanum carbonate at doses up to 2000 mg/kg/day was associated with a dose-dependent accumulation of lanthanum particularly in the liver and femur. Epithelial hyperplasia was observed in the gastric mucosa at doses of 500 mg/kg/day or higher in rodents. No gastric pathology occurred in dogs, but there was a dose-related increase in lanthanum concentration in the femur at the end of the 52-week treatment period.

Repeat-dose intravenous toxicity studies of 4 weeks duration with lanthanum chloride exposed rats and dogs to peak plasma lanthanum concentrations that were approximately 1500 times (rats, 0.3 mg/kg/day) or 20 000 times (dogs, 1.0 mg/kg/day) higher than in patients (assuming a human C_{max} of 1.06 ng/mL after 1000 mg of lanthanum carbonate dihydrate TID). No adverse effects occurred in rats. Chronic hepatitis was present in all male and female dogs given 1 mg/kg/day.

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.

Carcinogenicity: Oral administration of lanthanum carbonate to rats for up to 104 weeks, at doses up to 1500 mg/kg/day, revealed no evidence of carcinogenic potential. In mice, oral administration of lanthanum carbonate for up to 99 weeks at a dose of 1500 mg/kg/day was associated with an increased incidence of gastric glandular adenomas. There were no treatment effects on the incidences of malignant tumors.

Immunotoxicity: Specific immunotoxicity studies have not been performed.

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 2000 mg/kg/day.

In addition, lanthanum chloride, administered intravenously, was shown to be non-clastogenic in a bone marrow micronucleus test and in a liver unscheduled DNA synthesis assay in rats at doses up to 0.1 mg/kg/day, a dose that produced plasma lanthanum concentrations >2000 times the peak human plasma concentration.

Reproductive and Developmental Toxicology: In pregnant rats, oral administration of lanthanum carbonate at doses up to 2000 mg/kg/day resulted in no evidence of harm to the fetus. There was an increased incidence of observations of small pups in the group treated at 2000 mg/kg/day. In pregnant rabbits, oral administration of lanthanum carbonate at a dose of 1500 mg/kg/day was associated with a

reduction in maternal body weight gain, food consumption, fecal production, increased pre- and post-implantation losses, reduced fetal weights, and delayed fetal ossification.

Oral administration of lanthanum carbonate to rats from implantation through lactation at 2000 mg/kg/day caused delayed eye opening, reduction in body weight gain, and delayed sexual development (preputial separation and vaginal opening) of the offspring.

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

17 SUPPORTING PRODUCT MONOGRAPHS

1. FOSRENOL® (chewable tablets, 250 mg, 500 mg, 750 mg, and 1000 mg), submission control number (270959), Product Monograph, Takeda Canada Inc., (April 06, 2023)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrNAT-LANTHANUM
Lanthanum carbonate dihydrate chewable tablets

Read this carefully before you start taking **NAT-LANTHANUM** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **NAT-LANTHANUM**.

What is NAT-LANTHANUM used for?
NAT-LANTHANUM is used to lower blood phosphorus levels. It is used in adults with end-stage kidney disease who are on dialysis.

How does NAT-LANTHANUM work?
NAT-LANTHANUM binds to phosphate in your gut. This lowers the amount of phosphate that is absorbed from the food you eat.

What are the ingredients in NAT-LANTHANUM?
Medicinal ingredients: Lanthanum carbonate dihydrate
Non-medicinal ingredients: Colloidal silicon dioxide, dextrates (hydrated), hydroxy propyl cellulose, magnesium stearate and talc.

NAT-LANTHANUM comes in the following dosage forms:
Chewable tablets: 250 mg, 500 mg, 750 mg and 1000 mg

Do not use NAT-LANTHANUM if:
- you have a blockage in the intestine;
- you have severe constipation;
- you have hypophosphatemia. This is when blood phosphate levels are low;
- you are allergic to lanthanum carbonate or any of the ingredients in NAT-LANTHANUM.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take NAT-LANTHANUM. Talk about any health conditions or problems you may have, including if you:
- have had a blockage in the intestine, tear of the intestine wall, constipation, or diabetes,
- have had previous abdominal surgery,
- have suffered from peritonitis (inflammation of the abdomen) or diverticulitis (infection or inflammation in the intestine),
- have previously had stomach or intestinal cancer,
- suffer from acute peptic ulcer, ulcerative colitis, or Crohn's disease,
- suffer from liver problems or a blocked bile duct,
- are taking chelation therapy.

Other warnings you should know about:
Treatment with NAT-LANTHANUM increases your risk for constipation, blockage in the intestine and tearing of the intestine wall. These could cause you to be hospitalized. You might need surgery. Watch for signs of stomach or intestinal problems, which can include constipation, abdominal pain and bloating. Tell your doctor about these symptoms, if they happen to you.

NAT-LANTHANUM may build up in your bones and digestive tract. Your healthcare professional will consider this, if you need to take NAT-LANTHANUM for a long time.

Your healthcare professional may recommend that you follow a specific diet. This diet would control the fluids you drink and the amount of phosphate you eat.

Pregnancy and breastfeeding:

- Taking NAT-LANTHANUM during pregnancy is not recommended.
- It is not known if NAT-LANTHANUM passes into breast milk.
- Talk to your healthcare professional:
    - if you are pregnant or are planning to become pregnant.
    - about the best ways to feed your baby while you are taking NAT-LANTHANUM.

X-rays: Tell your doctor that you are taking NAT-LANTHANUM before having an X-ray of your abdomen. This is because NAT-LANTHANUM may affect the results.

Endoscopy: Tell your doctor that you are taking NAT-LANTHANUM before your gastrointestinal endoscopy. This is because NAT-LANTHANUM might leave lanthanum deposits in the digestive tract.

Blood tests: You will need to have regular blood tests to measure the amount of phosphate in your blood.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with NAT-LANTHANUM:

- Some medicines used to treat bacterial infections including ciprofloxacin.
- A medicine used to treat an underactive thyroid called levothyroxine.
- Some medicines should not be taken within 2 hours before or 2 hours after taking NAT-LANTHANUM. These include:
    - Two medicines used to treat bacterial infections, including acne called tetracycline and doxycycline.
    - A medicine used to treat malaria called chloroquine.
    - A medicine used to treat rheumatoid arthritis and malaria called hydroxychloroquine.
    - A medicine used to treat fungal infections called ketoconazole.

How to take NAT-LANTHANUM:

- Take exactly as directed by your healthcare professional.
- Your healthcare professional will tell you how much NAT-LANTHANUM to take.
- Divide your daily dose as directed by your healthcare professional.
- Take your NAT-LANTHANUM with or right after eating a meal.

- Chew tablets completely before swallowing. Do NOT swallow tablets whole. This is because serious stomach and intestinal problems can happen including nausea, vomiting, abdominal cramps and diarrhea.
- If you cannot chew tablets, crush them completely before swallowing.

Usual dose:
Usual starting dose: 750 mg to 1500 mg per day.
Maintenance dose: 1500 mg to 3000 mg per day.

Your healthcare professional will tell you how much NAT-LANTHANUM to take and will adjust your dose every 2 to 3 weeks to find the dose that is right for you.

Overdose:
The symptoms of overdose may be headache, nausea and vomiting.

If you think you, or a person you are caring for, have taken too much NAT-LANTHANUM, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you miss a dose, take your next dose at your usual time with or right after a meal. Taking a dose without food may lead to nausea and vomiting. Do not take two doses at once to make up for a missed dose.

What are possible side effects from using NAT-LANTHANUM?
These are not all the possible side effects you may feel when taking NAT-LANTHANUM. If you experience any side effects not listed here, contact your healthcare professional.

- nausea
- vomiting
- trouble with digestive system
- gas
- burping
- indigestion or heartburn
- diarrhea or soft stool
- constipation
- abdominal cramps
- increased or loss of appetite
- weight loss
- headache
- respiratory infection
- throat infection
- infection of the inside of the nose
- high blood sugar levels
- low or high blood phosphate levels
- increased liver enzyme levels
- increased blood aluminum levels
- strange tastes
- dry mouth
- thirst
- difficulty swallowing
- sores in the mouth
- tooth problems and injury
- hair loss
- itching
- skin redness
- rash
- increased sweating
- muscle and joint pain
- fatigue
- malaise
- pain
- dizziness

NAT-LANTHANUM can cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Allergic skin reaction: rash, hives, itching		√	
COMMON			
Dialysis graft complications including occlusion (problems with the dialysis access tube): fever, chills, blood or pus draining from access tube, sudden swelling or bulging, redness and pain around graft access, hand or arm is numb, cool or pale			√
Hypotension (low blood pressure): dizziness, fainting, light-headedness		√	
UNCOMMON			
Chest pain		√	
Eosinophilia (abnormal white blood cell count): abdominal pain, rash, weight loss, wheezing		√	
Gastrointestinal obstruction complete (ileus) or incomplete (subileus) [blockage that stops or impairs passage of contents of intestines]: abdominal bloating, abdominal pain, swelling or cramps, constipation, vomiting			√
Hyperparathyroidism (enlarged parathyroid glands): tingling or burning of fingertips, toes or lips, muscle aches, cramps or spasms, fatigue, weakness, painful menstrual period, dry skin, brittle nails, depression or anxiety		√	
Hypocalcemia (low blood calcium levels): confusion or memory loss, muscle cramps or spasms, numbness and tingling in hands, feet or face, weak and brittle nails		√	
Osteoporosis (bone disease): back pain, loss of height over time, stooped posture, broken bones		√	
Peripheral edema (swelling of limbs)		√	
RARE			

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Gastrointestinal perforation (tear or hole in the wall of the stomach or intestine): sudden severe abdominal pain, swelling and or bloating of the stomach area, nausea, vomiting, fever and chills			√
UNKNOWN FREQUENCY			
Product residue present in digestive tract: (detectable with endoscopy) abdominal bloating, abdominal pain, swelling or cramps, constipation, vomiting		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store between 15-30°C.

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

If you want more information about NAT-LANTHANUM:
- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website http://www.natcopharma.ca/, or by calling 1-800-296-9329.

This leaflet was prepared by:

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