AUSTRALIAN PRODUCT INFORMATION

FOSRENOL® (lanthanum carbonate hydrate) – chewable tablets

1 NAME OF THE MEDICINE

Lanthanum carbonate hydrate.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

FOSRENOL is presented as chewable tablets. Each tablet contains lanthanum carbonate hydrate corresponding to 500 mg, 750 mg or 1000 mg lanthanum.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Tablet, chewable

- FOSRENOL 500 mg: White, round, bevel-edged flat tablets debossed with 'S405/500' on one side.
- FOSRENOL 750 mg: White to off-white round, flat bevel-edged tablets debossed on one side with 'S405' above '750'.
- FOSRENOL 1000 mg: White to off-white round, flat bevel-edged tablets debossed on one side with 'S405' above '1000'.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment of hyperphosphataemia in adults with chronic renal failure on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD)

4.2 DOSE AND METHOD OF ADMINISTRATION

Patients should adhere to recommended diets in order to control phosphate and fluid intake.

FOSRENOL tablets must be chewed completely before swallowing. The tablets may be crushed as an aid to chewing. Intact tablets must not be swallowed whole.

Adults, including elderly (>65 years)

For patients taking FOSRENOL for the first time, the starting dose may be determined individually based on serum phosphate concentration as indicated in the following table (Table 1):

Table 1

Pre-treatment serum phosphate level	Recommended initial daily dose of FOSRENOL
>1.8 and ≤2.4 mmol/L	750 mg
>2.4 and ≤2.9 mmol/L	1500 mg
>2.9 mmol/L	2250 mg

FOSRENOL should be taken with or immediately after food, with the daily dose divided between meals, i.e. three times daily. 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.

Control of serum phosphate level has been demonstrated at doses from 750 mg with most patients achieving acceptable serum phosphate levels at 1500 – 3000 mg lanthanum per day.

Hepatic impairment

The effect of hepatic impairment on FOSRENOL pharmacokinetics has not been formally assessed. Due to its mechanism of action and the lack of liver metabolism, doses in hepatic impairment should not be modified, but patients should be monitored carefully (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 5.2 PHARMACOKINETIC PROPERTIES).

Paediatric use

The safety and efficacy of FOSRENOL has not been established in patients below the age of 18 years.

4.3 CONTRAINDICATIONS

Hypersensitivity to lanthanum or any of the excipients in the product.
Hypophosphataemia.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Tissue deposition of lanthanum, particularly in bone, liver and the stomach wall, has been shown with FOSRENOL in animal studies. Deposition of lanthanum in bone has been studied (see Effects on Bone). Results from long-term studies (Studies 301, 303 and 307) demonstrated that bone lanthanum concentration had no apparent effect on bone health or treatment outcome for up to 4.5 years. There is no clinical data examining the potential deposition of lanthanum in other tissues. The long-term clinical effects of lanthanum deposition in tissues are not known. The risk benefit of longer-term therapy with FOSRENOL should be considered.

Gastrointestinal Disorders

There have been cases of gastrointestinal obstruction, ileus, subileus, and gastrointestinal perforation reported in association with lanthanum, some requiring surgery or hospitalisation (See Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Some of the cases are found to have lanthanum deposition or Product residue in the gastrointestinal tract.

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.

During treatment with lanthanum carbonate, 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 lanthanum carbonate should be re-evaluated in patients who develop severe constipation or other severe gastrointestinal signs and symptoms.

Patients with acute peptic ulcer, ulcerative colitis, Crohn's disease or bowel obstruction were not included in clinical studies with FOSRENOL.

FOSRENOL tablets must be chewed completely and not swallowed whole. Serious gastrointestinal complications have been reported in association with unchewed or incompletely chewed tablets (See Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Use in hepatic impairment

Lanthanum is not metabolised by liver enzymes but it is most likely excreted in the bile. Conditions resulting in a marked reduction of bile flow may be associated with incrementally slower elimination of lanthanum, which may result in higher plasma levels and increased tissue deposition of lanthanum (see Section 5.2 PHARMACOKINETIC PROPERTIES). Caution should therefore be exercised in these patients and monitoring of liver function may be required.

Use in renal impairment

Patients with renal insufficiency may develop hypocalcaemia. FOSRENOL does not contain calcium. Serum calcium levels should therefore be monitored at the usual time intervals for this patient population and appropriate supplements given.

Use in the elderly

No data available.

Paediatric use

The efficacy and safety of FOSRENOL has not been studied in children, therefore, the consequence of lanthanum deposition in growing bones is not known.

Effects on laboratory tests

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

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The drug interaction profile of FOSRENOL is characterised by the potential of lanthanum to bind to drugs with anionic functions (e.g. carboxyl, carbonyl and hydroxyl groups).

Lanthanum carbonate may increase gastrointestinal pH.

It is recommended that compounds, which are known to interact with antacids, should not be taken within 2 hours of dosing with FOSRENOL (e.g. chloroquine, hydroxychloroquine and ketoconazole).

Serum levels of fat-soluble vitamins A, D, E and K, were not affected by FOSRENOL administration in clinical studies.

Lanthanum carbonate is not a substrate for cytochrome P450. *In vitro* tests indicate that no significant inhibition of the activities of the major human cytochrome P450 isoenzymes, CYP1A2, CYP2D6, CYP3A4, CYP2C9 or CYP2C19 is expected at therapeutic concentrations. Lanthanum is extensively bound in human plasma and isolated human

plasma protein preparations, including albumin, transferrin and alpha-1-acid glycoprotein (99.7 to >99.9%).

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

***In Vitro*- Interactions with other Medicines**

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.

The therapeutic activity of FOSRENOL depends on the acidity of the gastric environment. The potential for drugs which alter gastric acidity (for example proton-pump inhibitors) to alter the therapeutic activity of FOSRENOL has not been examined in trials but should be considered.

***In Vivo*- Interactions with other Medicines**

In healthy subjects, the absorption and pharmacokinetics of a single dose of 1000 mg of FOSRENOL is unaffected by co-administration of citrate. No clinically-relevant effects of lanthanum were found on the absorption and pharmacokinetic profiles 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.

Co-administration of FOSRENOL with quinolone antibiotics may reduce the extent of 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. It is recommended that oral quinolone formulations are taken at least 2 hours before or 4 hours after FOSRENOL.

Phosphate binders (including FOSRENOL) have been shown to reduce the absorption of levothyroxine. The bioavailability of levothyroxine was decreased by approximately 40% when taken together with FOSRENOL. Consequently, thyroid hormone replacement therapy should not be taken within 2 hours of dosing with FOSRENOL and closer monitoring of TSH levels is recommended in patients receiving both medicinal products.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no human data on the effects of lanthanum carbonate on fertility. Lanthanum carbonate administered to female and male rats prior to and throughout mating at oral doses up to 2000 mg/kg/day (half the clinical exposure based on AUC at 3000 mg/day) did not alter mating or fertility.

Use in pregnancy

(Category B3)

There was no evidence of teratogenicity in rats or rabbits following oral administration of lanthanum carbonate during the period of organogenesis at doses up to 2000 (rat) and 1500 (rabbit) mg/kg/day (0.5-1.2 times the clinical exposure based on AUC at 3000 mg/day). Increased implantation loss, and delayed skeletal ossification occurred in rabbits at ≥1500 mg/kg/day, in association with maternal toxicity. There are no adequate data from the use of FOSRENOL in pregnant women. The safety of lanthanum carbonate in human pregnancy has not been established. FOSRENOL should not be used during pregnancy unless the potential benefit justifies the potential risk.

Use in lactation

There is some evidence that lanthanum can be excreted in human breast milk. The excretion of lanthanum in milk following oral treatment with lanthanum carbonate has not been studied in animals. Post-natal development was delayed in the offspring of rats receiving oral doses of lanthanum carbonate at 2000 mg/kg/day. Women taking FOSRENOL should stop breastfeeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

FOSRENOL may induce dizziness and vertigo, which may impair the ability to drive and use machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The safety of FOSRENOL for use in patients with end-stage renal failure (ESRF) in both hemodialysis and peritoneal dialysis patients was initially examined in three short-term, placebo-controlled, double-blind studies, three long-term, comparator-controlled studies, and three long- term open-label studies. These studies have provided a total safety database of 1754 patients treated with lanthanum carbonate hydrate and represents a mean exposure of 272.1 days (median 184.0 days, range 1-1123 days).

The most common adverse events (≥5% in either treatment group) in two long-term open-label phase III trials that included 1215 patients treated with lanthanum carbonate hydrate and 944 with alternative therapy are detailed in Table 2.

The adverse events in the long-term, open label, active controlled, study of FOSRENOL vs. alternative therapy (Study 307) have been adjusted for mean exposure differences between the treatment groups (with a mean exposure of 1.0 years 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. Incidence of Treatment-Emergent Adverse Events that occurred in ≥5% of Patients (in Either Treatment Group) and in Both Comparative Studies 307 and 301.

	Study 307 %		Study 301 %	
	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
Diarrhoea	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	7	5	6
Rhinitis	4	6	7	6
Hypercalcaemia	4	8	0	20

* Alternative therapy included calcium carbonate, calcium acetate, sevelamer, aluminium based phosphate binders.

Overall, approximately 24% of all ESRF patients who participated in these clinical studies reported a drug related adverse reaction, as determined by the investigator. No individual ADR was reported at a frequency greater than 10%. The most commonly reported adverse drug reactions, with the exception of headache, are gastrointestinal in nature. Gastrointestinal reactions were the most common leading to discontinuation. Gastrointestinal reactions can be minimized by taking FOSRENOL with food and generally abated with time with continued dosing (see Section 4.2 DOSAGE AND METHOD OF ADMINISTRATION).

Table 3 presents the very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000 to <1/100) and rare (≥ 1/10,000 to < 1/1,000) reactions reported: with FOSRENOL in clinical trials to date.

Table 3. Adverse Drug Reactions Associated with FOSRENOL

Organ System	Very Common Reactions	Common Reactions	Uncommon Reactions	Rare	Unknown
Infections and Infestations			Gastroenteritis, laryngitis		
Blood and lymphatic system disorders			Eosinophilia		
Endocrine disorders			Hyperparathyroidism		
Metabolism and nutrition disorders		Hypocalcaemia	Hypercalcaemia, hyperglycaemia, hyperphosphataemia, hypophosphataemia, anorexia, appetite increased		
Nervous system disorders	Headache		Dizziness, taste alteration		
Ear and Labyrinth disorders			Vertigo		
Gastrointestinal disorders	Abdominal pain, diarrhoea,	Constipation, dyspepsia, flatulence	Eructation, indigestion, irritable bowel syndrome, dry	Intestinal perforation	Product residue present

	nausea, vomiting		mouth, oesophagitis, stomatitis, stools loose, tooth disorder, gastro-intestinal disorder NOS*, ileus, subileus, intestinal obstruction		
Skin and subcutaneous tissue disorders			Alopecia, sweating increased		
General Disorders and Administrative Site Conditions				Tooth injury	
Musculoskeletal and connective tissue disorders			Arthralgia, myalgia, osteoporosis		
General disorders			Asthenia, chest pain, fatigue, malaise, peripheral oedema, pain, thirst		
Investigations			Elevated Aluminum, increase in GGT, increases in hepatic transaminases, alkaline phosphatase increased, weight decrease		

* Not otherwise specified.

Post marketing experience

During post-approval use of FOSRENOL, cases of allergic skin reactions (including skin rashes, urticaria and pruritus) have been reported which show a close temporal relationship to lanthanum carbonate therapy. In clinical trials, allergic skin reactions were seen in both FOSRENOL and placebo/active comparator groups at a frequency of very common (≥1/10).

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

Transient QT changes have been observed but these were not associated with any adverse events.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

The symptoms associated with overdose are known adverse reactions such as headache, nausea and vomiting. As FOSRENOL is only pharmacologically active within the gut, supportive therapy is recommended for overdose.

For information on the management of overdose, contact the Poisons Information Centre telephone: 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

FOSRENOL (lanthanum carbonate hydrate) has been developed as a dietary phosphate-binding agent. Phosphate absorption from the gastrointestinal tract is effectively decreased by the formation of highly insoluble complexes that are largely unable to pass through the wall of the gastrointestinal tract and are eliminated by excretion.

FOSRENOL is indicated for the treatment of hyperphosphataemia. FOSRENOL contains lanthanum carbonate hydrate. The activity of lanthanum carbonate as a phosphate binder is dependent on the high affinity of lanthanum ions, which are released from the carbonate salt in the acid environment of the upper gastrointestinal tract, for dietary phosphate. Insoluble lanthanum phosphate is formed which reduces the absorption of phosphate from the gastro-intestinal tract.

Several studies have shown that lanthanum can be used to control hyperphosphataemia associated with chronic renal failure through dose titration and that effect is maintained with long-term use. A lower incidence of hypercalcaemia was reported with FOSRENOL (0.4%) compared with calcium-based binders (20.2%) in comparative studies.

Serum PTH concentrations may fluctuate depending on a patient's serum calcium, phosphate and vitamin D status. FOSRENOL has not been shown to have any direct effects on PTH secretion.

Clinical trials

A total of 1130 patients with chronic renal failure treated with maintenance haemodialysis or CAPD were studied in two phase II and two phase III studies (LAM-IV-202, 204, 301 and 302). Three studies were placebo controlled (1 fixed dose and 2 titrated dose designs) and one included calcium carbonate as an active comparator. During these studies, 1016 patients received lanthanum carbonate, 267 received calcium carbonate and 95 received placebo.

The first phase III study (301) was a two-part study designed to assess the reduction of serum phosphate by FOSRENOL compared to calcium carbonate. The study had 2 parts: Part 1 was a 5-week titration phase after randomization to FOSRENOL or calcium carbonate where patients were titrated to a target phosphate level of 1.8 mmol/L. Part 2 was a 20-week maintenance phase where patients maintained their doses of binder and plasma phosphate levels assessed. The study endpoints were % patients achieving target phosphate levels at the end of the titration and maintenance periods. The plasma phosphate levels from this study are presented in Table 4. Serum phosphate levels were reduced to target levels of 1.8 mmol/L at the end of the 5 week titration period, in 58% of the lanthanum group compared with 70% of the calcium carbonate group. Following 25 weeks of treatment, the proportions controlled were 66% (lanthanum carbonate) and 64% (calcium carbonate).

Table 4: Plasma phosphate (mmol/L) levels in clinical study 301.

		Treatment Group			
Weeks on treatment	**Visit**	**Lanthanum**		**Calcium**	
		N	**Mean (SD)**	**N**	**Mean (SD)**
0	1	504	2.67 (0.66)	254	2.69 (0.63)
5 (Endpoint 1)[1]	6	453	1.87 (0.52)	209	1.66 (0.48)
25 (Endpoint 2)[2]	11	222	1.73 (0.46)	122	1.72 (0.48)

[1] Primary endpoint, after completion of titration phase

[2] Secondary endpoint, after completion of maintenance phase.

The second Phase III study (302) was a double-blind, placebo-controlled study designed to assess the maintenance in reduction in serum phosphate levels after an open-label titration phase with FOSRENOL to achieve a target phosphate concentration of 1.8 mmol/L. This was followed by a 4-week double-blind phase where patients were randomised to continue to receive FOSRENOL or a comparable number of placebo tablets. The endpoint of this study was the plasma phosphate concentrations after 4 weeks of treatment on FOSRENOL or placebo. A total of 93 patients completed the open-label phase and were randomised to FOSRENOL or placebo. The plasma phosphate levels at the end of the open-label titration and at each week of the double-blind study are presented in Table 5.

Table 5: Plasma phosphate levels (mmol/L) in clinical study 302

	Treatment Group			
	Lanthanum		**Placebo**	
	N	**Mean (SD)**	**N**	**Mean (SD)**
End of Titration[1]	46	1.81 (0.54)	43	1.77 (0.48)
RMP Week 1	46	1.87 (0.54)	43	2.23 (0.54)
RMP Week 2	44	1.86 (0.48)	43	2.41 (0.55)
RMP Week 3	41	1.78 (0.45)	39	2.46 (0.65)
RMP Week 4	41	1.89 (0.50)	38	2.49 (0.61)
Study Endpoint[2]	**44**	**1.91 (0.53)**	**43**	**2.54 (0.63)**

[1] End of open-label titration phase (Randomisation)
[2] Study endpoint (LOCF) double-blind, placebo phase.
RMP = Randomised Maintenance Phase.

A Phase II randomised, double-blind, placebo-controlled study (SPD405-206) was also conducted in chronic kidney disease stage 3 and 4 patients not undergoing dialysis but requiring treatment with phosphate binders. The primary endpoint was achievement of a target serum phosphate concentration of ≤1.49 mmol/L. Eighty patients were randomised to receive FOSRENOL vs 41 patients on placebo. The ITT population consisted of 56 patients on FOSRENOL vs 34 patients on placebo (there were a large number of discontinuations mainly due to patients' baseline not being above the target serum phosphate level after the washout phase). Patients were treated for up to 8 weeks. At the end of the study the mean dose of FOSRENOL was 2645.3 mg/day. 44.6% of FOSRENOL patients had achieved the target phosphate concentration compared to 26.5% of patients on placebo. The difference was not statistically significant (p=0.12). The mean change from baseline to end of treatment for serum phosphate in the FOSRENOL group was -0.18 mmol/L compared to -0.06 mmol/L in the placebo group.

Hyperphosphataemia

Lanthanum has been demonstrated to be an effective binder of dietary phosphate for use in controlling the hyperphosphataemia of chronic renal failure. Multiple studies have shown that lanthanum can reliably be used to achieve serum phosphate reductions to target levels through dose titration and to effectively maintain control of serum phosphate levels with long-term use. Maintenance of target phosphate levels was shown to be similar between lanthanum and calcium treatments.

The lowest effective dose of lanthanum that is effective in the control of serum phosphate levels was established to be approximately 750 mg/day. Doses of up to 3000 mg lanthanum resulted in a reduction of serum phosphate to within target control levels in most patients.

No difference in level of control was observed between those patients on haemodialysis and those receiving CAPD. In addition, no difference in the effectiveness of lanthanum carbonate administration was noted between patients under or over 65 years of age.

Effects on Bone

Overall, FOSRENOL and standard treatments, including calcium carbonate, produced similar effects on the bones of dialysis patients.

Results from histology and histomorphometry of human biopsy samples evaluated to date from the three clinical studies (Study 301 where patients had been treated with lanthanum carbonate for up to 4.5 years, Studies 303 and 307) showed no evidence of osteomalacia or other adverse bone pathology. In Study 303, a randomised study to investigate the effect of FOSRENOL with calcium carbonate, results showed that FOSRENOL produced marginally greater improvements towards normal values than calcium carbonate for many of the bone primary and secondary response variables in addition to the general improvements in bone growth and turnover parameters. In Study 307, a study where patients had been treated for 2 years, no statistical differences in bone parameters between patients randomised to receive standard therapy or FOSRENOL were observed. Analysis of data from paired bone biopsies (at baseline and at one or two years) in patients randomised to either FOSRENOL or calcium carbonate in Study 303 and patients randomised to either FOSRENOL or alternative therapy in Study 307, showed no differences in the development of mineralisation defects between the groups. An analysis of adverse events in the bone study participants in these studies did not show any increase in adverse events related to the musculoskeletal system, including fractures. FOSRENOL, therefore, does not appear to harm bone following treatment for up to 4.5 years.

5.2 PHARMACOKINETIC PROPERTIES

As binding between lanthanum and dietary phosphorus occurs in the lumen of the stomach and upper small intestine, the therapeutic effectiveness of FOSRENOL is not dependent on levels of lanthanum in the plasma.

Lanthanum is present in the environment. Measurement of background levels in non-lanthanum treated chronic renal failure patients during Phase III clinical trials revealed concentrations of <0.05 to 0.90 ng/mL in plasma, and <0.006 to 1.02 μg/g in bone biopsy samples.

Absorption

Lanthanum carbonate has low aqueous solubility (<0.01 mg/mL at pH 7.5) and is minimally absorbed following oral administration. Absolute oral bioavailability is estimated to be <0.002% in humans.

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 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 3 times daily, the mean (± sd) peak plasma concentration was 1.06 (± 1.04) ng/mL, and mean AUC_{last} was 31.1 (± 40.5) ng.h/mL. Regular blood level monitoring in 1707 renal dialysis patients taking lanthanum carbonate for up to 2 years showed no increase in plasma lanthanum concentrations over this time period.

Distribution

Orally administered lanthanum is distributed predominantly within the gastrointestinal tract. The small fraction absorbed is extensively bound to human plasma proteins (>99.7%), and binding is high capacity and non-specific. In long-term animal studies, at oral doses up to 17 times a human dose of 3000 mg/day, lanthanum concentrations in the majority of tissues were less than 1 μg/g. Concentrations in brain and cerebrospinal fluid (CSF) were below or around the assay quantification limit (0.01 μg/g for brain and 0.05 ng/mL for CSF) and median steady state concentrations were up to 8.2 μg/g in bone, 11.1 μg/g in liver and 2.2 mg/g in the stomach wall. Rodents, but not dogs, treated at doses 4 times the human dose of 3000 mg/day showed submucosal inflammation and epithelial hyperplasia of the stomach. No other adverse effects were associated with these concentrations. Lanthanum levels in these tissues dissipated very slowly after the cessation of oral dosing, with a half-life >26 weeks. Cases of lanthanum deposition in gastrointestinal mucosa, mainly after long term use, have been reported. The clinical significance of this is yet unknown.

Metabolism

Lanthanum is not metabolised. 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.

Excretion

Lanthanum is excreted mainly in the faeces (>90%) with only around 0.000031% of an oral dose excreted via the urine in healthy subjects.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

In vitro assays for gene mutations (bacteria and CHO cells) and *in vivo* studies for chromosomal or DNA damage did not provide evidence of genotoxic potential. An *in vitro* chromosome aberration assay in CHO cells had an equivocal outcome.

Carcinogenicity

Lanthanum carbonate, at doses 13-times higher than the clinical dose of 3000 mg/day, caused a slight increase in gastric adenomas in mice. This response was considered to be an exacerbation of spontaneous stomach pathology and secondary to changes in the gastric environment caused by lanthanum carbonate administration. Gastric pathology was confined to rodents.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

FOSRENOL tablets also contain the excipients dextrates, silicon dioxide and magnesium stearate.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

36 months from date of manufacture.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25˚C.

6.5 NATURE AND CONTENTS OF CONTAINER

FOSRENOL is supplied as chewable tablets in white cylindrical HDPE bottles fitted with polypropylene caps and is available in the following presentation and pack sizes:

FOSRENOL 500 mg: 45 tablets per bottle; 2 bottles per pack (pack of 90 tablets).

FOSRENOL 750 mg: 15 tablets per bottle; 6 bottles per pack (pack of 90 tablets).

FOSRENOL 1000 mg: 15 tablets per bottle; 6 bottles per pack (pack of 90 tablets).

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

$La_2(CO_3)_3.xH_2O$ = 457.85 (anhydrous), on average x = 4.5 moles of water.

CAS number

54451-24-0

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (S4)

8 SPONSOR

Takeda Pharmaceuticals Australia Pty Ltd
Level 39
225 George Street
Sydney, NSW 2000
Australia
Telephone: 1800 012 612
www.takeda.com/en-au

9 DATE OF FIRST APPROVAL

8 November 2005

10 DATE OF REVISION

25 October 2021

Summary table of changes

Section Changed	Summary of new information
4.4	New statement under Gastrointestinal Disorders
4.8	New ADR added to Table 3