FOSRENOL

Lanthanum carbonate hydrate

Chewable Tablet

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each chewable tablet contains lanthanum carbonate hydrate corresponding to 250 mg, 500 mg, 750 mg or 1000 mg lanthanum. For excipients, see **"List of excipients"**.

PHARMACEUTICAL FORM

Chewable tablet.
250 mg tablets: white, round, beveled-edge flat tablets embossed with 'S405/250' on one side.
500 mg tablets: white, round, beveled-edge flat tablets embossed with 'S405/500' on one side.
750 mg tablets: white, round, beveled-edge flat tablets embossed with 'S405/750' on one side.
1000 mg tablets: white, round, beveled-edge flat tablet embossed with 'S405/1000' on one side.

CLINICAL PARTICULARS

Therapeutic indications

Fosrenol is indicated as a phosphate binding agent for use in the control of hyperphosphataemia in chronic renal failure patients on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD).

Posology and method of administration

Fosrenol is for oral administration. Tablets must be chewed and not swallowed whole. The experience with therapy beyond two years is limited (see **"Special warnings and precautions for use").** The risk/benefit from long-term administration over two years should be carefully considered.

Adults, including elderly (>65 years)

Fosrenol should be taken with or immediately after food, with the daily dose divided between meals. Patients should adhere to recommended diets in order to control phosphate and fluid intake. Fosrenol is presented as a chewable tablet therefore avoiding the need to take additional fluid. 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 starting from 750 mg per day. The maximum dose studied in clinical trials, in a limited number of patients, in 3750 mg. Patients who respond to lanthanum therapy, usually achieve acceptable serum phosphate levels at doses of 1500-3000 mg lanthanum per day.

Children and Adolescents

The safety and efficacy of Fosrenol has not been established in patients below the age of 18 years (see **"Special warnings and precautions for use"**).

Hepatic impairment

The effect of hepatic impairment on Fosrenol pharmacokinetics has not been assessed. Due 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 **"Special precautions and warnings for use"** and **"Pharmacokinetic properties"**).

Contraindications

Hypersensitivity to lanthanum carbonate hydrate or to any of the excipients. Hypophosphataemia.

Special warnings and precautions for use

Tissue deposition of lanthanum has been shown with Fosrenol in animal studies. in 105 bone biopsies from patients treated with Fosrenol, some for up to 4.5 years, rising levels of lanthanum were noted over time (see **"Pharmacodynamic properties"**). No clinical data are available on deposition of lanthanum in other human tissues. Safety data exceeding 24 months are currently limited. The risk/benefit from longer-term administration should be carefully considered. Patients with acute peptic ulcer, ulcerative colitis, Crohn's disease or bowel obstruction were not included in clinical studies with Fosrenol. Fosrenol should be used in these patients following careful assessment of benefit and risk. Patients with renal insufficiency may develop hypocalcaemia. Fosrenol does not contain calcium. Serum calcium levels

should therefore be monitored at regular time intervals for this patient population and appropriate supplements given. No pharmacokinetic data are available in patients with 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 "**Pharmacokinetic properties"** and **"Preclinical safety data"**). Caution should, therefore, be exercised in these patients, and monitoring of liver function may be required. Safety and efficacy of Fosrenol have not been established in paediatric patients; use in children is not recommended (see **"Posology and method of administration")**. Fosrenol should be discontinued if hypophosphataemia develops. Abdominal x-rays of patients taking Lanthanum Carbonate may have a radio-opaque appearance typical of an imaging agents.

Interactions with other medicinal products and other forms of interaction

Lanthanum carbonate hydrate may increase gastric 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). In healthy subjects, the absorption and pharmacokinetics of lanthanum were not affected by co-administration of citrate. Serum levels of fat-soluble vitamins A, D, E and K, were not affected by Fosrenol administration in clinical studies. Human volunteer studies have shown that co-administration of Fosrenol with digoxin, warfarin or metoprolol does not produce clinically-relevant changes in the pharmacokinetic profiles of these drugs. In simulated gastric juice, lanthanum carbonate hydrate did not form insoluble complexes with warfarin, digoxin, frusemide, phenytoin, metoprolol or enalapril, suggesting a low potential to affect the absorption of these drugs. However, interactions with drugs such as tetracycline, doxycycline and the floxacins are theoretically possible and if these compounds are to be co-administered, it is recommended that they not be taken within 2 hours of dosing with Fosrenol. Lanthanum carbonate hydrate is not a substrate for cytochrome P450 and does not significantly inhibit the activities of the major human cytochrome P450 isoenzymes, CYP1A2, CYP2D6, CYP3A4, CYP2C9 or CYP2C19 in vitro.

Pregnancy and lactation

There are no adequate data from the use of Fosrenol in pregnant women. One study in rats showed reproductive foetotoxicity (delayed eye opening and sexual maturation) and reduced pup weights at high doses (see **"Pre-clinical safety data"**). The potential risk for humans is unknown. Fosrenol is not recommended for use during pregnancy. It is unknown whether lanthanum is excreted in human breast milk. The excretion of lanthanum in milk has not been studied in animals. Caution should be used in taking a decision whether to continue/discontinue breast feeding or to continue/discontinue therapy with Fosrenol, taking into account the potential benefit of breast feeding to the child and the potential benefit of Fosrenol therapy to the nursing mother.

Effects on ability to drive and use machines

Fosrenol may induce dizzines and vertigo, which may impair the ability to drive and use machinery.

Undesirable effects

The safety of Fosrenol for use in patients with end-stage renal failure (ESRF) on maintenance haemodialysis and peritoneal dialysis has been examined in three short-term, placebo-controlled, double-blind studies, three long-term, comparator controlled studies, and three long-term open-label studies. Three studies have provided a total safety database of 1754 patients treated with lanthanum carbonate hydrate with 495 patients with more than 1 year of treatment and 130 patients with more than 2 years of treatment and represents a mean exposure of 272.1 days (median 184.0 days, range 1-1123 days).

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 hypocalcaemia, are gastrointestinal in nature; these are minimized by taking Fosrenol with food and generally abated with time with continued dosing (see **"Posology and method of administration"**).

Organ System	Common Reactions (>1/100, <1/10)	Uncommon Reactions (>1/1,000 to <1/100)
Infections and Infestations		Gastroenteritis, laryngitis
Blood and lymphatic system disorders		Eosinophilia
Endocrine disorders		Hyperparathyroidism
Metabolism and nutrition disorders		Dizziness, headache, taste alteration
Ear and Labyrinth disoreders	Abdominal pain, constipation, diarrhoea, dyspepsia, flatulence, nausea, vomiting	Eructation, indigestion, irritable bowel syndrome, dry mouth, oesophagitis, stomatitis, loose stools, tooth disorders, gastrointestinal disorder NOS+
Skin and subcutaneous tissue disorders		Alopecia itching, pruritus, erythematous rash, sweeting increased
Musculoskeletal and connective tissue disorders		
General disorders		Asthenia, chest pain, fatigue, malaise, peripheral oedema, pain, thrist
Investigations		Blood aluminium increased, increase in GGT, increases in hepatic transaminase, alkaline phosphatase increased, weight decrease

*Not otherwise specified

[Boots code]

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 an increase of cardiac adverse events.

Overdose
No case of overdose has been reported. The highest daily dose of lanthanum administered to healthy volunteers during Phase I studies was 4718 mg given for 3 days. The adverse events seen were mild to moderate and included nausea and headache.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for treatment of hyperkalaemia and hyperphosphataemia.
ATC code: V03A E03

Fosrenol contains lanthanum carbonate hydrate. The activity of lanthanum carbonate hydrate 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 stomach, for dietary phosphate. Insoluble lanthanum phosphate is formed which reduces the absoption of phosphate from gastro-intestinal tract.

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. 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 176 received placebo.

Two-placebo controlled, randomised studies enrolled patients on dialysis after a washout from previous phosphate binders. After titration of lanthanum carbonate to achieve a serum phosphate level between 1.3 and 1.8 mmol/L in one study (doses up to 2250 mg/day), or ≤1.8 mmol/L in a second study (doses up to 3000 mg/day), patients were randomised to lanthanum carbonate or palcebo as maintenance treatment. After the 4-week randomised placebo-controlled phase, the serum phosphate concentration rose between 0.5 and 0.6 mmol/L in the placebo group, in both studies, relative to patients who remained on lanthanum carbonate therapy. There were 61% patients on lanthanum carbonate who maintained their response, compared to 23% on placebo.

The active comparator study demonstrated that serum phosphate levels were reduced to target levels of 1,8 mmol/l at the end of the 5 week titration period, in 51% of the lanthanum group compared with 57% of the calcium carbonate group. AT week 25 the percentage of randomised patients showing controlled serum phosphate levels was similar in the two treatment groups, 29% on lanthanum and 30% on calcium carbonate (using a missing=failure approach). Mean serum phosphate levels were reduced by a similiar amount in both treatment groups.

Further long-term extension studies have demonstrated maintenance of phosphate reduction for some patients following continued administration of at least 2 years of lanthanum carbonate.

Hypercalcaemia was reported in 0.4% of patients with Fosrenol compared with 20.2% on calcium-based binders 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 serum PTH concentrations.

In the long-term bone studies a trend towards increasing bone lanthanum concentrations with time in the control population was observed from the averaged data, the median rising 3-fold from a baseline of 53 mg/kg at 24 months. In patients treated with lanthanum carbonate, the bone lanthanum concentration increased during the first 12 months of lanthanum carbonate treatment up to a median of 1328 mg/kg (range 122-5513 mg/kg). Median and range concentrations at 18 and 24 months were similiar to 12 months. The median at 54 months was 4246 mg/kg (range 1673-9792 mg/kg).

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

Pharmacokinetic properties

As binding between lanthanum and dietary phosphorus occurs in the lumen of the stomatch 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 carbonate hydrate-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 1.0 mg/g in bone biopsy samples.

Absorption

Lanthanum carbonate hydrate 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 hydrate for up to 2 years showed no increase in plasma lanthanum concentrations over this time period.
Distribution
Lanthanum does not accumulate in plasma in patients or in animals after repeated oral administration of lanthanum carbonate hydrate. The small fraction of orally administered lanthanum absorbed is extensively bound to plasma proteins (>99.7%).
and in animal studies, was widely distributed to systemic tissues, predominantly bone, liver and the gastrointestinal tract, including the mesenteric lymph nodes. In long-term animal studies lanthanum concentrations in several tissues, including the gastrointestinal tract, bone and liver increased over time to levels several orders of magnitude above those in plasma. An apparent steady-state level of lanthanum was attained in some tissues, e.g. the liver whereas levels in gastrointestinal tract increased with duration of treatment. 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 % retained in bone ≤100% (rat) and ≤87% (dog), and in the liver ≤6% (rat) and ≤82% (dog). No adverse effects were associated with the tissue deposition of lanthanum seen in long-term animal studies with high oral doses of lanthanum carbonate (see **"Preclinical safety data")** (See **"Pharmacodynamic properties** for information regarding changes in lanthanum concentrations in bone biopsies taken from renal dialysis patients after one year of treatment with lanthanum containing versus calcium conaining phosphate binders).
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.
Elimination
Lanthanum is excreted mainly in the faeces with only around 0.000031% of an oral dose excreted via the urine in healthy subjects (renal clearance approximately 1 mL/min, representing <2% of total plasma clearance).
After intravenous administration to animals, lanthanum is excreted mainly in the faeces (74% of the dose), both via the bile and direct transfer across the gut wall.
Renal excretion was a minor route.

Preclinical safety data

Preclinical data reveal no special hazards for humans based on conventional studies of safety pharmacology, repeated dose toxicity or genotoxicity.
Lanthanum carbonate hydrate reduced gastric acidity in the rat in a safety pharmacology study.
In rats administered high doses of lanthanum carbonate hydrate from day 6 of gestation to day 20 post partum there were no maternal effects, but reduced pup weight and delays in some developmental markers (eye and vaginal opening) were seen. In rabbits given high daily doses of lanthanum carbonate hydrate during gestation, maternal toxicity with reduced maternal food intake and body weight gain, increased pre- and post- implantation losses and decreased pup weight were seen.
Lanthanum carbonate hydrate was not carcinogenic in mice or rats. In mice, an increase in gastric glandular adenomas was seen in the high-dose group (1500 mg/kg/day). The neoplastic response in the mouse is considered to be related to an exacerbation of spontaneous pathological stomach changes and to be of little clinical significance.
Studies in animals have shown deposition of lanthanum in tissues, mainly the gastrointestinal tract, mesenteric lymph nodes, liver and bone (see **"Pharmacokinetic properties"**). However, life-time

studies in healthy animals do not indicate a hazard for man from the use of Fosrenol. Specific immunotoxicity studies have noot been performed.

PHARMACEUTICAL PARTICULARS
List of excipients
Dextrates (hydrated)
Colloidal anhydrous silica
Magnesium stearate.

Incompatibilities
Not applicable

Shelf life
2 years.

Special precautions for storage
Store below 25^0 C. Keep in the original container.

Nature and contents of container
White cylindrical HDPE bottles containing a rayon coil fitted with a tamper evident, child resistant polypropylene screw cap.

Pack sizes
250 mg tablets: Box, 1 Bottles @ 90 tablets.
500 mg tablets: Box, 1 Bottles @ 45 tablets.
750 mg tablets: Box, 6 Bottles @ 15 tablets.
1000 mg tablets: Box, 6 Bottles @ 15 tablets.

Special precautions for disposal
No special requirements.

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