SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Fosrenol 750 mg oral powder
Fosrenol 1000 mg oral powder

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains 750 mg lanthanum (as lanthanum carbonate hydrate).
Each sachet contains 1000 mg lanthanum (as lanthanum carbonate hydrate).

Excipient(s) with known effect:
Each sachet of 750 mg also contains 641.7 mg dextrates, containing glucose.
Each sachet of 1000 mg also contains 855.6 mg dextrates, containing glucose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral Powder.

White to off-white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Fosrenol is indicated as a phosphate binding agent for use in the control of hyperphosphataemia in chronic renal failure (CRF) patients on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD). Fosrenol is also indicated in adult patients with chronic kidney disease not on dialysis with serum phosphate levels ≥1.78 mmol/L in whom a low phosphate diet alone is insufficient to control serum phosphate levels.

4.2 Posology and method of administration

Fosrenol is for oral administration.

Fosrenol oral powder is intended to be mixed with a small quantity of soft food (e.g. applesauce or other similar food product) and consumed immediately (within 15 minutes). The sachet must not be opened until ready to use. Once mixed with food, Fosrenol oral powder must not be stored for future use. Fosrenol oral powder is insoluble and must not be dissolved in liquid for administration.

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 an oral powder intended to be mixed with soft food, therefore avoiding the need to take additional fluid. Serum phosphate levels should be monitored and the

dose of Fosrenol titrated every 2 to 3 weeks until an acceptable serum phosphate level is reached, with regular monitoring thereafter. Dose titration may be performed with the chewable tablet presentation as these are available in a number of strengths allowing for smaller increases in dose.

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, is 3750 mg. Patients who respond to lanthanum therapy, usually achieve acceptable serum phosphate levels at doses of 1500 – 3000 mg lanthanum per day.

Paediatric population
The safety and efficacy of Fosrenol in children and adolescents below the age of 18 years have not been established.

Hepatic impairment
The effect of hepatic impairment on Fosrenol pharmacokinetics has not been 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 sections 4.4 and 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Hypophosphataemia.

4.4 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 section 5.1). Cases of lanthanum deposition in gastrointestinal mucosa, mainly after long term use, have been reported. Lanthanum deposition in gastroduodenal mucosa is demonstrated endoscopically as whitish lesions of different sizes and shapes. Also, various 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.

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).
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 alert for signs and symptoms of gastrointestinal disorders, especially constipation and abdominal pain/distension 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.

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.

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 sections 5.2 and 5.3). As the liver is the principal organ of elimination of absorbed lanthanum monitoring of liver function tests is recommended.

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 agent.

Patients with rare glucose-galactose malabsorption should not take this medicine.

4.5 Interaction 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, furosemide, phenytoin, metoprolol or enalapril, suggesting a low potential to affect the absorption of these drugs.

However, interactions 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.

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 floxacin 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. 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.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy
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 section 5.3). The potential risk for humans is unknown. Fosrenol is not recommended for use during pregnancy.

Breast-feeding
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.

Fertility
There are no fertility data available on lanthanum carbonate in humans. In rat toxicology studies, lanthanum carbonate had no adverse effects on fertility.

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 machines.

4.8 Undesirable effects

The safety of lanthanum carbonate for use in patients has been examined in a number of clinical studies. The most commonly reported adverse drug reactions, with the exception of headache and allergic skin reactions, are gastrointestinal in nature; these are minimised by taking Fosrenol with food and generally abated with time with continued dosing (see section 4.2).

The following convention was used for frequency of adverse drug reactions: Very common (≥1/10); Common (≥1/100 to < 1/10); Uncommon (≥ 1/1,000 to < 1/100); Rare (≥1/10,000 to < 1/1,000); Very rare (< 1/10,000), not known (cannot be estimated from the available data).

Infections and Infestations	
Uncommon	Gastroenteritis, laryngitis
Blood and lymphatic system disorders	
Uncommon	Eosinophilia

Endocrine disorders	
Uncommon	Hyperparathyroidism
Metabolism and nutrition disorders	
Common	Hypocalcaemia
Uncommon	Hypercalcaemia, hyperglycaemia, hyperphosphataemia, hypophosphataemia, anorexia, appetite increased
Nervous system disorders	
Very Common	Headache
Uncommon	Dizziness, taste alteration
Ear and Labyrinth disorders	
Uncommon	Vertigo
Gastrointestinal disorders*	
Very Common	Abdominal pain, diarrhoea, nausea, vomiting
Common	Constipation, dyspepsia, flatulence
Uncommon	Ileus, subileus, intestinal obstruction, irritable bowel syndrome, oesophagitis, stomatitis, loose stools, indigestion, gastrointestinal disorder (not otherwise specified), dry mouth, tooth disorder, eructation
Rare	Intestinal perforation
Skin and subcutaneous tissue disorders	
Uncommon	Alopecia, sweating increased
Musculoskeletal and connective tissue disorders	
Uncommon	Arthralgia, myalgia, osteoporosis
General disorders and administration site conditions	
Uncommon	Asthenia, chest pain, fatigue, malaise, peripheral oedema, pain, thirst.
Investigations	
Uncommon	Blood aluminium increased, increase in GGT, increases in hepatic transaminases, alkaline phosphatase increased, weight decrease.
Not known	Product residue present[1]

[1]See Lanthanum deposition in gastrointestinal mucosa warning in section 4.4 Special warnings and precautions for use

*In a clinical trial in healthy subjects, the incidence of gastrointestinal adverse events was higher after administration of the oral powder formulation of Fosrenol (13 subjects, 18.3%) than after chewable tablets (4 subjects, 6.6%).

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 an increase of cardiac adverse events.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

https://sideeffects.health.gov.il

4.9 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 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 absorption of phosphate from the gastro-intestinal tract.

In healthy subjects administered Fosrenol 3 times daily for 3 days as oral powder or chewable tablets, Fosrenol oral powder was found to be pharmacodynamically equivalent to Fosrenol chewable tablets, based on urinary phosphate excretion.

Information from studies using chewable tablets
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 placebo 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 similar 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 μg/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 μg/kg (range 122-5513 μg/kg). Median and range concentrations at 18 and 24 months were similar to 12 months. The median at 54 months was 4246 μg/kg (range 1673-9792 μg/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 the groups.

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 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 μg/g in bone biopsy samples.

Absorption

In healthy subjects administered Fosrenol 3 times daily for 3 days as oral powder or chewable tablets, the systemic exposure to lanthanum (based on AUC_{0-48} and C_{max}) was approximately 30% higher and more variable following administration of Fosrenol oral powder than Fosrenol chewable tablets. By comparison with data for the chewable tablet (see below), the systemic exposure arising from the oral powder is still consistent with an absolute bioavailability <0.002%.

Information from studies using chewable tablets
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 section 5.3) (See section 5.1 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 containing phosphate binders).

Biotransformation
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 1mL/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.

5.3 Preclinical safety data

Preclinical data reveal no special hazards for humans based on conventional studies of safety pharmacology, repeated dose toxicity, fertility 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 section 5.2). However, life-time studies in healthy animals do not indicate a hazard for man from the use of Fosrenol. Specific immunotoxicity studies have not been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dextrates (hydrated)
Colloidal anhydrous silica
Magnesium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

750 mg - 2.1 g oral powder
1000 mg - 2.8 g oral powder
in sachets formed from a polyethylene terephthalate/aluminium/polyethylene laminate.

Pack size: 90 sachets (Outer carton contains 9 cartons of 10 sachets).

6.6 Special precautions for disposal

No special requirements.

7 MANUFACTURER

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8 REGISTRATION HOLDER

Takeda Israel Ltd.,25 Efal st., Petach Tikva 4951125

9 REGISTRATION NUMBERS

Fosrenol 750 mg oral powder 153-35-34025
Fosrenol 1000 mg oral powder 153-36-34022

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