SEVELAMER CARBONATE FOSFAMER

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800 mg Film-Coated Tablet
Phosphate Binder

FORMULATION:
Each film-coated tablet contains:
Sevelamer carbonate ..... 800 mg

PRODUCT DESCRIPTION:
White coloured, elongated shaped, biconvex, both side plain film-coated tablet.

PHARMACOLOGICAL PROPERTIES:
Pharmacodynamic properties
Pharmacokinetic studies have not been carried out with sevelamer carbonate. Sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, is not absorbed from the gastrointestinal tract, as confirmed by an absorption study in healthy volunteers.
Mechanism of action
Sevelamer Carbonate contains sevelamer, a non-absorbed phosphate binding crosslinked polymer, free of metal and calcium. Sevelamer contains multiple amines separated by one carbon from the polymer backbone which become protonated in the stomach. These protonated amines bind negatively charged ions such as dietary phosphate in the intestine.
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Pharmacodynamic effect
By binding phosphate in the gastrointestinal tract and decreasing absorption, sevelamer lowers the phosphorus concentration in the serum. Regular monitoring of serum phosphorus levels is always necessary during phosphate binder administration.
Pediatric population
The safety and effectiveness of sevelamer carbonate in hyperphosphatemic pediatric patients with CKD was evaluated in a multicenter study with a 2-week, randomised, placebo-controlled, fixed dose period (FDP) followed by a 6-month, single-arm, open-label, dose titration period (DTP). A total of 101 patients (6 to 18 years old with a BSA range of 0.8 m^2 to 2.4 m^2) were randomised in the study. Forty-nine (49) patients received sevelamer carbonate and 51 received placebo during the 2-week FDP. Thereafter all patients received sevelamer carbonate for the 26-week DTP. The study met its primary endpoint, meaning Sevelamer carbonate reduced serum phosphorus by an LS mean difference of 0.90 mg/dL compared to placebo, and secondary efficacy endpoints. In pediatric patients with hyperphosphatemia secondary to CKD, sevelamer carbonate significantly reduced serum phosphorus levels compared to placebo during a 2-week FDP. The treatment response was maintained in the pediatric patients who received sevelamer carbonate during the 6-month open-label DTP. 27% of pediatric patients reached their age appropriate serum phosphorus level at end of treatment. These figures were 23% and 15% in the subgroup of patients on hemodialysis and peritoneal dialysis, respectively. The treatment response during the 2-week FDP was not affected by BSA, in contrast however, no treatment response was observed in pediatric patients with qualifying phosphorus levels <7.0 mg/dL. Most of adverse events reported as related, or possibly related, to sevelamer carbonate were gastrointestinal in nature. No new risks or safety signals were identified with the use of sevelamer carbonate during the study.

Pharmacokinetic properties
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In a clinical trial of one year, no evidence of accumulation of sevelamer was seen. However, the potential absorption and accumulation of sevelamer during long-term chronic treatment (> one year) cannot be totally excluded.

INDICATIONS:
Sevelamer Carbonate is indicated for the control of hyperphosphatemia in adult patients receiving hemodialysis or peritoneal dialysis.
Sevelamer Carbonate is also indicated for the control of hyperphosphatemia in adult patients with chronic kidney disease (CKD) not on dialysis with serum phosphorus ≥ 1.78 mmol/L.
Sevelamer Carbonate should be used within the context of a multiple therapeutic approach, which could include calcium supplement, 1,25-dihydroxy Vitamin D3 or one of its analogues to control the development of renal bone disease.

DOSAGE AND ADMINISTRATION:
Starting dose
The recommended starting dose of Sevelamer carbonate is 2.4 g or 4.8 g per day based on clinical needs and serum phosphorus level. Sevelamer Carbonate must be taken three times per day with meals.

Serum phosphorus level in patients	Total daily dose of sevelamer carbonate to be taken over 3 meals per day
1.78 – 2.42 mmol/l (5.5 – 7.5 mg/dl)	2.4 g*
> 2.42 mmol/L (> 7.5 mg/dl)	4.8 g*

*Plus subsequent titrating, see section " Titration and maintenance"

For patients previously on phosphate binders (sevelamer hydrochloride or calcium based), Sevelamer Carbonate should be given on a gram for gram basis with monitoring of serum phosphorus levels to ensure optimal daily doses.

Titration and maintenance
Serum phosphorus levels must be monitored and the dose of Sevelamer carbonate titrated by 0.8 g three times per day (2.4 g/day) increments every 2-4 weeks until an acceptable serum phosphorus level is reached, with regular monitoring thereafter.

Patients taking Sevelamer carbonate should adhere to their prescribed diets.

In clinical practice, treatment will be continuous based on the need to control serum phosphorus levels and the daily dose is expected to be an average of approximately 6 g per day.

Special populations
Elderly population
No dosage adjustment is necessary in the elderly population.

Hepatic impairment
No studies have been performed in patients with hepatic impairment.

Pediatric population
The safety and efficacy of Sevelamer Carbonate in children below the age of 6 years or in children with a BSA below 0.75m^2 have not been established.

The safety and efficacy of Sevelamer Carbonate in children over 6 years of age and a BSA >0.75 m^2 have been established.

For pediatric patients the oral suspension should be administered, as tablet formulations are not appropriate for this population.

Method of administration
Oral use.
Tablet should be swallowed intact and should not be crushed, chewed, or broken into pieces prior to administration. Sevelamer Carbonates hould be taken with food and not on an empty stomach.

CONTRAINDICATIONS
- Hypersensitivity to the active substance or to any of the excipients.
- Hypophosphatemia.
- Bowel obstruction.

WARNINGS AND PRECAUTIONS:
The safety and efficacy of Sevelamer carbonate have not been established in adult patients with chronic kidney disease not on dialysis with serum phosphorus <1.78 mmol/L. Therefore, it is currently not recommended for use in these patients.
The safety and efficacy of Sevelamer carbonate have not been established in patients with the following disorders:
- dysphagia
- swallowing disorders
- severe gastrointestinal motility disorders including untreated or severe gastroparesis, retention of gastric contents and abnormal or irregular bowel motion
- active inflammatory bowel disease
- major gastrointestinal tract surgery

Treatment of these patients with Sevelamer Carbonate should only be initiated after careful benefit/risk assessment. If the therapy is initiated, patients suffering from these disorders should be monitored. Sevelamer Carbonate treatment should be reevaluated in patients who develop severe constipation or other severe gastrointestinal symptoms.

Intestinal obstruction and ileus/sub-ileus
In very are cases, intestinal obstruction and ileus/sub-ileus have been observed in patients during treatment with sevelamer hydrochloride (capsules/tablets), which contains the same active moiety as Sevelamer carbonate. Constipation may be a preceding symptom. Patients who are constipated should be monitored carefully while being treated with Sevelamer Carbonate. The treatment should be re-evaluated in patients who develop severe constipation or other severe gastrointestinal symptoms.

Fat-soluble vitamins and folate deficiency
Patients with CKD may develop low levels of fat-soluble vitamins A, D, E and K, depending on dietary intake and the severity of their disease. It cannot be excluded that sevelamer carbonate can bind fat-soluble vitamins contained in ingested food. In patients not taking supplemental vitamins but on sevelamer, serum vitamin A, D, E and K status should be assessed regularly. It is recommended that vitamin supplements be given if necessary. It is recommended that CKD patients not on dialysis are given vitamin D supplements (approximately 400 IU of native vitamin D daily) which can be part of a multivitamin preparation to be taken apart from their dose of Sevelamer carbonate. In patients undergoing peritoneal dialysis additional monitoring of fat-soluble vitamins and folic acid is recommended, since vitamin A, D, E and K levels were not measured in a clinical study in these patients.

There is at present insufficient data to exclude the possibility of folate deficiency during long term Sevelamer carbonate treatment. In patients not taking supplemental folic acid but on sevelamer, folate level should be assessed regularly.

Hypocalcemia/hypercalcemia
Patients with CKD may develop hypocalcemia or hypercalcemia. Sevelamer carbonate does not contain any calcium. Serum calcium levels should therefore be monitored at regular intervals and elemental calcium should be given as a supplement if required.

Metabolic acidosis
Patients with CKD are predisposed to developing metabolic acidosis. As part of good clinical practice, monitoring of serum bicarbonate levels is therefore recommended.

Peritonitis
Patients receiving dialysis are subject to certain risks for infection specific to dialysis modality. Peritonitis is a known complication in patients receiving peritoneal dialysis and in a clinical trial with sevelamer hydrochloride, a greater number of peritonitis cases were reported in the sevelamer group than in the control group. Patients on peritoneal dialysis should be closely monitored to ensure the correct use of appropriate aseptic technique with the prompt recognition and management of any signs and symptoms associated with peritonitis.

Swallowing and choking difficulties
Uncommon reports of difficulty swallowing the Sevelamer Carbonate tablet have been reported. Many of these cases involved patients with co-morbid conditions including swallowing disorders or oesophageal abnormalities. Proper swallowing ability should be carefully monitored in patients with co-morbid conditions. The use of sevelamer carbonate powder in patients with a history of difficulty swallowing should be considered.

Hypothyroidism
Closer monitoring of patients with hypothyroidism co-administered with sevelamer carbonate and levothyroxine is recommended.

Hyperparathyroidism
Sevelamer carbonate is not indicated for the control of hyperparathyroidism. In patients with secondary hyperparathyroidism Sevelamer carbonate should be used within the context of a multiple therapeutic approach, which could include calcium as supplements, 1,25-dihydroxy Vitamin D3 or one of its analogues to lower the intact parathyroid hormone (iPTH) levels.

Inflammatory gastrointestinal disorders
Cases of serious inflammatory disorders of different parts of the gastrointestinal tract (including serious complications such as hemorrhage, perforation, ulceration, necrosis, colitis and colonic/caecal mass) associated with the presence of sevelamer crystals have been reported. Inflammatory disorders may resolve upon sevelamer discontinuation. Sevelamer carbonate treatment should be re-evaluated in patients who develop severe gastrointestinal symptoms.

PREGNANCY AND LACTATION:
Pregnancy
There are no or limited amount of data from the use of sevelamer in pregnant women. Animal studies have shown some reproductive toxicity when sevelamer was administered to rats at high doses. Sevelamer has also been shown to reduce the absorption of several vitamins including folic acid. The potential risk to humans is unknown. Sevelamer carbonate should only be given to pregnant women if clearly needed and after a careful risk/benefit analysis has been conducted for both the mother and the fetus.

Breastfeeding
It is unknown whether sevelamer/metabolites are excreted in human milk. The non-absorbed nature of sevelamer indicates that excretion of sevelamer in breast milk is unlikely. A decision on whether to continue/discontinue breastfeeding or to continue/discontinue therapy with Sevelamer carbonate should be made taking into account the benefit of breast-feeding to the child and the benefit of Sevelamer carbonate therapy to the woman.

Fertility
There are no data from the effect of sevelamer on fertility in humans. Studies in animals have shown that sevelamer did not impair fertility in male or female rats at exposures at a human equivalent dose 2 times the maximum clinical trial dose of 13 g/day, based on a comparison of relative BSA.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Sevelamer Carbonate has no or negligible influence on the ability to drive and use machines.

DRUG INTERACTIONS:
Dialysis
Interaction studies have not been conducted in patients on dialysis.

Ciprofloxacin
In interaction studies in healthy volunteers, sevelamer hydrochloride, which contains the same active moiety as Sevelamer carbonate, decreased the bioavailability of ciprofloxacin by approximately 50% when co-administered with sevelamer hydrochloride in a single dose study. Consequently, sevelamer carbonate should not be taken simultaneously with ciprofloxacin.

Ciclosporin, mycophenolate mofetil and tacrolimus in transplant patients
Reduced levels of ciclosporin, mycophenolate mofetil and tacrolimus have been reported in transplant patients when co-administered with sevelamer hydrochloride without any clinical consequences (e.g. graft rejection). The possibility of an interaction cannot be excluded and a close monitoring of blood concentrations of ciclosporin, mycophenolate mofetil and tacrolimus should be considered during the use of combination and after its withdrawal.

Levothyroxine
Very rare cases of hypothyroidism have been reported in patients co-administered with sevelamer hydrochloride, which contains the same active moiety as Sevelamer carbonate, and levothyroxine. Closer monitoring of thyroid stimulating hormone (TSH) levels is therefore recommended in patients receiving sevelamer carbonate and levothyroxine.

Anti-arrhythmics and anti-seizure medicinal products
Patients taking anti-arrhythmic medicinal products for the control of arrhythmias and anti-seizure medicinal products for the control of seizure disorders were excluded from clinical trials. Therefore, possible reduction in absorption cannot be excluded. The anti-arrhythmic medical product should be taken at least one hour before or three hours after Sevelamer carbonate, and blood monitoring can be considered.

Proton pump inhibitors
During post-marketing experience, very rare cases of increased phosphate levels have been reported in patients taking proton pump inhibitors co-administered with Sevelamer carbonate. Caution should be exercised when prescribing PPI to patients concomitantly treated with Renvela. The phosphate serum level should be monitored and the Sevelamer Carbonate dosage adjusted consequently.

Bioavailability
Sevelamer carbonate is not absorbed and may affect the bioavailability of other medicinal products. When administering any medicinal product where a reduction in the bioavailability could have a clinically significant effect on safety or efficacy, the medicinal product should be administered at least one hour before or three hours after Sevelamer carbonate, or the physician should consider monitoring blood levels.

Digoxin, warfarin, enalapril or metoprolol
In interaction studies in healthy volunteers, sevelamer hydrochloride, which contains the same active moiety as Sevelamer carbonate, had no effect on the bioavailability of digoxin, warfarin, enalapril or metoprolol.

ADVERSE DRUG REACTIONS:
Summary of the safety profile
The most frequently occurring (≥ 5% of patients) adverse reactions were all in the gastrointestinal disorders system organ class. Most of these adverse reactions were mild to moderate in intensity.

Tabulated list of adverse reactions
The safety of sevelamer (as either carbonate and hydrochloride salts) has been investigated in numerous clinical trials involving a total of 969 haemodialysis patients with treatment duration of 4 to 50 weeks (724 patients treated with sevelamer hydrochloride and 245 with sevelamer carbonate), 97 peritoneal dialysis patients with treatment duration of 12 weeks (all treated with sevelamer hydrochloride) and 128 patients with CKD not on dialysis with treatment duration of 8 to 12 weeks (79 patients treatment with sevelamer hydrochloride and 49 with Sevelamer carbonate).

Adverse reactions that occurred during clinical trials or that were spontaneously reported from post-marketing experience are listed by frequency in the table below. The reporting rate is classified as 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).

MedDRA System Organ Class	Very common	Common	Very rare	Not known
Immune system disorders			Hypersensitivity*	
Gastrointestinal disorders	Nausea, vomiting, upper abdominal pain, constipation	Diarrhea , dyspepsia, flatulence, abdominal pain		Intestinal obstruction, ileus/sub -ileus, intestinal perforation [1], gastrointestinal hemorrhage [*1], intestinal ulceration* [1], gastrointestinal necrosis* [1], colitis* [1], intestinal mass* [1]
Skin and subcutaneous tissue disorders				Pruritus, rash
Investigations				Crystal deposit intestine* [1]

*post-marketing experience

[1]See inflammatory gastrointestinal disorders warning in section.

Pediatric population
In general, the safety profile for children and adolescents (6 to 18 years of age) is similar to the safety profile for adults.

OVERDOSE AND TREATMENT:
Sevelamer hydrochloride, which contains the same active moiety as Sevelamer carbonate, has been given to normal healthy volunteers in doses of up to 14 grams per day for eight days with no adverse reactions. In CKD patients, the maximum average daily dose studied was 14.4 grams of Sevelamer carbonate in a single daily dose.

The symptoms observed in case of overdose are similar to adverse reactions, including mainly constipation and other known gastrointestinal disorders.

Appropriate symptomatic treatment should be provided.

CAUTION:
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

ADR REPORTING STATEMENT:
For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph.
Seek medical attention immediately at the first sign of any adverse drug reaction.

STORAGE CONDITION:
Store at temperatures not exceeding 30°C.

KEEP ALL MEDICINES OUT OF REACH OF CHILDREN.

AVAILABILITY:
Alu/Alu Blister Pack x 10's (Box of 30's)

DRP-14864-01
Date of First Authorization: July 7, 2024
Date of Revision of Package Insert: August 5, 2024

"UNDER DRUG PRICE REGULATION
RETAIL PRICE NOT TO EXCEED Php 50.21"

Manufactured by :
STALLION LABOR ATORIES PVT . LTD.
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Dist: Ahmedabad, Gujarat, India

Imported by:
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