Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product

SEVCAR 800

2. Qualitative and quantitative composition

Each film-coated tablet contains 800 mg of sevelamer carbonate.

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated tablet.

A white to off white, coloured, modified capsule shaped, film-coated tablet.

4. Clinical particulars

4.1 Therapeutic indications

Sevelamer carbonate is indicated for the control of hyperphosphataemia in adult patients receiving haemodialysis or peritoneal dialysis.

Sevelamer carbonate is also indicated for the control of hyperphosphataemia in adult patients with chronic kidney disease not on dialysis with serum phosphorus levels ≥1.78 mmol/l.

Sevelamer carbonate should be used within the context of a multiple therapeutic approach, which could include calcium supplements, 1,25-dihydroxy vitamin D3 or one of its analogues to control the development of renal bone disease.

4.2 Posology and method of administration

Posology

The recommended starting dose of sevelamer carbonate for adults and elderly is 2.4 g or 4.8 g per day, based on clinical need and serum phosphorus level.

Serum phosphorus	**Recommended starting dose**
1.78 – 2.42 mmol/l (5.5 – 7.5 mg/dl)	2.4 g per day
> 2.42 mmol/l (> 7.5 mg/dl)	4.8 g per day

Sevelamer carbonate should be administered three times daily with meals.

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.

Dose titration and maintenance

Serum phosphorus levels should be monitored and the dose of sevelamer carbonate titrated by 0.8 g three times per day (2.4 g/day) increments every 2 to 4 weeks as necessary, until an acceptable serum phosphorus level is reached, with periodic 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
No dosage adjustment is necessary in the elderly population.

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

Paediatric population
The safety and efficacy of sevelamer carbonate in children below the age of 6 years or in children with a body surface area (BSA) below 0.75 m^2 have not been established. No data are available.

The safety and efficacy of sevelamer carbonate in children over 6 years of age and a BSA greater than 0.75 m^2 have been established. For paediatric patients, the oral suspension formulation should be administered, as tablet formulations are not appropriate for this population.

Method of administration
For oral use.

Tablets should be swallowed intact and should not be crushed, chewed, or broken into pieces prior to administration. Sevelamer carbonate should be taken with food and not on an empty stomach.

4.3 Contraindications
Sevelamer carbonate is contraindicated in patients with:
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Hypophosphataemia
- Bowel obstruction

4.4 Special warnings and precautions for use

The safety and efficacy of sevelamer carbonate have not been established in adult patients with chronic kidney disease not on dialysis with serum phosphorus below 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 therapy is initiated, patients suffering from these disorders should be monitored. Sevelamer carbonate treatment should be re-evaluated in patients who develop severe constipation or other severe gastrointestinal symptoms.

Intestinal obstruction and ileus/subileus

In very rare cases, intestinal obstruction and ileus/subileus have been observed with the use of sevelamer hydrochloride. Constipation may be a premonitory symptom. Patients experiencing constipation should be carefully monitored while on sevelamer carbonate. Severe constipation and other severe gastrointestinal adverse reactions should be evaluated promptly, and treatment interrupted if serious gastrointestinal complications develop.

Reduced vitamin absorption

Supplementation with vitamins A, D, E and K (fat-soluble vitamins), and folic acid should be considered for patients on dialysis who do not take multivitamin supplements, since sevelamer may bind these substances. It is recommended that vitamin status is assessed periodically. Chronic kidney disease patients not on dialysis should receive approximately 400 IU of native vitamin D per day, or as clinically indicated, in accordance with clinical practice guidelines for chronic kidney disease patients not on dialysis.

Hypocalcaemia/hypercalcaemia

Patients receiving sevelamer carbonate should have serum calcium levels monitored regularly. Elemental calcium supplements should be used to correct hypocalcaemia when necessary.

Metabolic acidosis

Patients with chronic kidney disease are prone to developing metabolic acidosis. Regular monitoring of serum bicarbonate levels is part of good clinical practice and is recommended for sevelamer carbonate as for any other phosphate binder.

Peritonitis
Peritoneal dialysis patients specifically may be at additional risk of developing peritonitis as a consequence of an increased incidence of peritonitis reported in sevelamer hydrochloride clinical studies. Adequate aseptic technique should always be used to prevent occurrences of peritonitis when carrying out associated procedures.

Difficulty swallowing
There have been uncommon reports of patients having difficulty swallowing the sevelamer carbonate tablet. Many, though not all, of these cases were reported in patients with concomitant conditions such as disorders of swallowing or oesophageal disorders. Caution should be applied when giving sevelamer carbonate tablets to patients with an impaired ability to swallow. Sevelamer powder for oral suspension may be considered for such patients.

Hypothyroidism
Caution should be exercised in patients receiving concomitant levothyroxine therapy since decreased levothyroxine efficacy has been reported very rarely in patients treated concomitantly with sevelamer, which in some instances resulted in hypothyroidism. Thyroid-stimulating hormone (TSH) levels should therefore be monitored more closely in patients receiving sevelamer and levothyroxine concomitantly.

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 intact parathyroid hormone (iPTH) levels.

Inflammation of the gastrointestinal tract
Cases of serious inflammatory disorders of the gastrointestinal tract (including severe complications such as haemorrhage, perforation, ulceration, necrosis, colitis, and caecum-related complications), some fatal, have been reported in association with sevelamer crystals in the gastrointestinal tract. Sevelamer treatment should be re-evaluated in patients who develop severe gastrointestinal symptoms.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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

Ciprofloxacin
In drug interaction studies with sevelamer hydrochloride, sevelamer decreased the bioavailability of ciprofloxacin by approximately 50% when co-administered as a single dose in a fasted state. Sevelamer carbonate should therefore not be administered simultaneously with ciprofloxacin.

Ciclosporin, mycophenolate mofetil and tacrolimus in transplant patients
Reduced trough levels of ciclosporin, mycophenolate mofetil, and tacrolimus have been reported in transplant patients concomitantly given sevelamer, without any clinical consequences (e.g. graft rejection) being reported. The possibility of interaction cannot be excluded, and careful monitoring of ciclosporin, mycophenolate mofetil, and tacrolimus blood concentrations should be considered during concomitant use with sevelamer.

Levothyroxine
Very rare cases of hypothyroidism have been reported in patients co-administered sevelamer and levothyroxine (see section 4.4).

Antiarrhythmics and anti-epileptic medicinal products
Patients with a history of arrhythmia or epilepsy were excluded from sevelamer clinical trials for reason of safety. Therefore, no data are available on the potential for interactions with antiarrhythmic medications used to treat cardiac arrhythmia, and antiepileptic medications used to treat seizure disorders. In view of the mode of action of sevelamer, consider not giving sevelamer carbonate simultaneously with these medicinal products (see also 'General note' below).

Proton pump inhibitors
Very rare cases of increased phosphate levels have been reported in patients using proton pump inhibitors concomitantly with sevelamer.

General note
Concomitant administration of sevelamer with oral medicinal products may reduce absorption of these medicinal products. Whenever, from a pharmacokinetic and/or pharmacodynamic point of view, a reduction in bioavailability of a medicinal product co-administered with sevelamer could have a clinically relevant 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 the blood levels of this medicinal product.

No effect on the bioavailability of digoxin, warfarin, enalapril, or metoprolol was observed when co-administered with sevelamer hydrochloride.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of sevelamer in pregnant women. Animal studies have shown reproductive toxicity at high doses. Sevelamer carbonate should only be given to pregnant women if clearly needed, after careful risk/benefit assessment for the mother and the foetus.

Breast-feeding
It is unknown whether sevelamer is excreted in human milk. Sevelamer is not systemically absorbed by the mother following oral administration; therefore excretion of sevelamer into human milk is unlikely to occur. Sevelamer carbonate can be used during breast-feeding only if the potential benefit outweighs the potential risk to the child. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from sevelamer carbonate therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
There are no data on the effect of sevelamer on human fertility. Sevelamer hydrochloride did not impair fertility in male or female rats at doses up to 4.5 g/kg/day (approximately 2 times the maximum recommended human dose based on body surface area).

4.7 Effects on ability to drive and use machines
Sevelamer has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects
Summary of the safety profile
The most frequently occurring adverse reactions (occurring in ≥5% of patients), are all classified within the System Organ Class (SOC) of gastrointestinal disorders. These adverse reactions were generally mild to moderate in intensity.

Tabulated list of adverse reactions

System organ class	Frequency	Adverse reaction
Immune system disorders	Very rare	Hypersensitivity*
Gastrointestinal disorders	Very common	Nausea, vomiting, upper abdominal pain, constipation
Gastrointestinal disorders	Common	Diarrhoea, dyspepsia, flatulence, abdominal pain
Gastrointestinal disorders	Not known	Intestinal obstruction, ileus/subileus, intestinal perforation, gastrointestinal haemorrhage, intestinal ulceration, gastrointestinal necrosis, colitis, intestinal mass (see section 4.4)
Skin and subcutaneous tissue disorders	Not known	Pruritus, rash
Investigations	Not known	Crystal deposit in the intestine*

* Identified through post-marketing surveillance.

Paediatric population
The overall safety profile of sevelamer carbonate in paediatric patients was similar to that observed in the adult population. The most frequently reported adverse events were also gastrointestinal in nature. No new safety signals were identified in the paediatric population.

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdose
Sevelamer has been administered to healthy volunteers at doses up to 14 g/day for 8 days without significant adverse effects. In chronic kidney disease patients, the maximum dose studied was 14.4 g/day of sevelamer carbonate. Symptoms of overdose would be expected to be limited to the gastrointestinal tract's undesirable effects noted in section 4.8, principally constipation. Treatment should be symptomatic and supportive.

5. Pharmacological properties

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: All other therapeutic products, drugs for treatment of hyperkalaemia and hyperphosphataemia, ATC code: V03A E02

Mechanism of action
Sevelamer carbonate contains sevelamer, a non-absorbed phosphate-binding crosslinked polymer, free of metal and calcium. It 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.

Pharmacodynamic effect
By binding phosphate in the gastrointestinal tract and decreasing its absorption, sevelamer lowers the phosphorus concentration in the serum. Regular monitoring of serum phosphorus levels is always necessary during phosphate binder administration.

Clinical efficacy
Two randomised crossover studies demonstrated that sevelamer carbonate tablets and sevelamer carbonate powder, both dosed three times daily, are therapeutically equivalent to sevelamer hydrochloride, at the same dose, with regard to serum phosphorus lowering effect in patients on haemodialysis. In one study, 79 haemodialysis patients received sevelamer carbonate tablets and sevelamer hydrochloride tablets, each for 8-week treatment periods; mean serum phosphorus

levels were 1.5 ± 0.3 mmol/l at the end of both treatment periods. In a second study, 31 hyperphosphataemic haemodialysis patients received sevelamer carbonate powder and sevelamer hydrochloride, each for 4-week treatment periods; mean serum phosphorus levels were 1.6 ± 0.5 mmol/l with sevelamer carbonate powder and 1.7 ± 0.4 mmol/l with sevelamer hydrochloride.

Effects on intact parathyroid hormone (iPTH)
In clinical trials in patients on haemodialysis, sevelamer alone did not demonstrate a consistent, clinically significant effect on intact parathyroid hormone (iPTH) levels. However, in patients on peritoneal dialysis, sevelamer produced reductions in iPTH similar to those observed with calcium acetate. Secondary hyperparathyroidism should continue to be managed with therapeutic measures such as calcium supplementation, 1,25-dihydroxy vitamin D3 or one of its analogues.

Effects on lipids
In clinical studies, sevelamer has consistently demonstrated reductions in total cholesterol and LDL-cholesterol of 15% to 39%. This effect is seen within 2 weeks of the start of treatment and is maintained on long-term treatment. Triglycerides, HDL-cholesterol and albumin levels remained unchanged.

Sevelamer effects on serum calcium
Sevelamer does not contain calcium. In clinical studies, sevelamer significantly decreased the incidence of hypercalcaemic episodes compared with patients using calcium-based phosphate binders. These effects were maintained during the 1-year follow-up study.

Paediatric population
The efficacy and safety of sevelamer carbonate were evaluated in a multicentre, 2-week randomised, double-blind, placebo-controlled fixed dose period (FDP), followed by a 6-month open-label dose titration period (DTP) in 101 paediatric chronic kidney disease patients aged 6 to 18 years and with a body surface area of 0.8 to 2.4 m^2. In the FDP, 49 patients received sevelamer carbonate and 51 received placebo; in the DTP, all patients received sevelamer carbonate. The study met its primary endpoint, demonstrating that sevelamer carbonate reduced serum phosphorus compared with placebo by 0.90 mg/dl during the FDP. The treatment response was maintained during the 6-month DTP, with 27% of patients reaching an age-appropriate serum phosphorus level (23% of the haemodialysis subgroup and 15% of the peritoneal dialysis subgroup). No treatment response was observed in patients with a baseline phosphorus level below 7.0 mg/dl. The majority of adverse events reported were gastrointestinal in nature, and no new safety signals were identified in this population.

5.2 Pharmacokinetic properties

No pharmacokinetic studies have been conducted with sevelamer carbonate. Sevelamer hydrochloride, which contains the same active moiety (sevelamer), is not absorbed from the gastrointestinal tract, as confirmed in an absorption study conducted in healthy volunteers.

A one-year clinical study did not show evidence of accumulation of sevelamer in patients. However, the possibility of some absorption and accumulation of sevelamer or its constituents during long-term chronic treatment (more than 1 year) cannot be totally excluded.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

In carcinogenicity studies with orally administered sevelamer hydrochloride, an increased incidence of urinary bladder transitional cell papilloma was observed in male rats at the high dose (approximately 2 times the maximum clinical trial dose) in a study using doses of 0.3 to 3 g/kg/day; no increase in tumour incidence was observed in a mouse study using doses up to 9 g/kg/day (approximately 3 times the maximum clinical trial dose).

In an in vitro mammalian cytogenetic test with metabolic activation, sevelamer hydrochloride produced a statistically significant increase in the incidence of structural chromosome aberrations. Sevelamer hydrochloride was not mutagenic in the Ames bacterial mutation assay.

Reduced absorption of vitamins D, E and K (fat-soluble vitamins) and folic acid have been observed with sevelamer hydrochloride in rats and dogs.

In pregnant rat studies, foetal skeletal ossification deficits were observed at intermediate and high doses; this effect may be secondary to sevelamer-induced reduction of vitamin D absorption. In pregnant rabbits given sevelamer hydrochloride by gavage, increased incidence of early resorptions was seen at the high dose (approximately 2 times the maximum clinical trial dose).

Sevelamer hydrochloride did not impair fertility in male or female rats at a dietary dose of 4.5 g/kg/day (approximately 2 times the maximum clinical trial dose).

6. Pharmaceutical particulars

6.1 List of excipients

Mannitol
Colloidal silicon dioxide
Zinc stearate (Veg 100 LB DRM)
Opadry white 06A580002

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
10 tablets are packed in Alu-Alu blister; such 5 blister along with the pack insert is packed in a carton.

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder
Emcure Pharmaceuticals Ltd.
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Bhosari, Pune – 411026
Country: India

8. Marketing authorisation number
H2024/CTD8244/16953

9. Date of first authorisation/renewal of the authorisation
4th June 2024

10. Date of revision of the text
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