

CAESEVA FILM COATED TABLET 800MG

1. NAME OF THE MEDICINAL PRODUCT

CAESEVA film coated tablet 800mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 800 mg sevelamer carbonate. For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablet.
Oval, white to off-white film coated tablets without scoring line. The tablets are debossed with ‘SVL’ on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

CAESEVA is also indicated for the control of hyperphosphataemia in adult patients with chronic kidney disease (CKD) not on dialysis with serum phosphorus ≥ 1.78 mmol/L.

CAESEVA 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.

4.2 Posology and method of administration

Because of the rapid disintegration of the carbonate salt tablet and its rapid reaction with the hydrochloric acid in the stomach, the dosing of CAESEVA is anticipated to be similar to that of the hydrochloride salt.

CAESEVA should be given three times a day with meals.

Patients Not Taking a Phosphate Binder. The recommended starting dose of CAESEVA is 800 to 1600 mg, which can be administered as one or two CAESEVA 800 mg Tablets, with meals based on serum phosphorus level. Table 1 provides recommended starting doses of CAESEVA for patients not taking a phosphate binder.

Table 1. Starting Dose for Patients Not Taking a Phosphate Binder

Serum Phosphorus	CAESEVA 800 mg
> 1.78 and < 2.42 mmol/L	1 tablet three times daily with meals
> 2.42 and < 2.91 mmol/L	2 tablets three times daily with meals
> 2.91 mmol/L	2 tablets three times daily with meals

Patients Switching from Sevelamer Hydrochloride. For patients switching from sevelamer hydrochloride, sevelamer carbonate should be prescribed on a gram per gram basis. Further titration to the desired phosphate levels may be necessary.

Patients Switching from Calcium Acetate. Table 2 gives recommended starting doses of CAESEVA based on a patient’s current calcium acetate dose.

Table 2. Starting Dose for Dialysis Patients Switching from Calcium Acetate to CAESEVA

Calcium Acetate 667 mg (Tablets per meal)	CAESEVA 800 mg (Tablets per meal)
1 tablet	1 tablet
2 tablets	2 tablets
3 tablets	3 tablets

Dose Titration for All Patients Taking CAESEVA. The dose should be increased or decreased by one tablet per meal at two week intervals, as necessary, with the goal of controlling serum phosphorus within the target range of 1.13 mmol/L to 1.78 mmol/L.

Method of administration

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

4.3 Contraindications

- 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 < 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 CAESEVA should only be initiated after careful benefit/risk assessment. If the therapy is initiated, patients suffering from these disorders should be monitored. CAESEVA treatment should be reevaluated 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 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 CAESEVA. 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.

Hypocalcaemia/hypercalcaemia

Patients with CKD may develop hypocalcaemia or hypercalcaemia. 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 CAESEVA 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 (see section 4.5).

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 haemorrhage, perforation, ulceration, necrosis, colitis and colonic/caecal mass) associated with the presence of sevelamer crystals have been reported (see section 4.8). Inflammatory disorders may resolve upon sevelamer discontinuation. Sevelamer carbonate treatment should be re-evaluated in patients who develop severe gastrointestinal symptoms.

Excipients

CAESEVA tablets contain 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

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. 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

Possible reduction in absorption cannot be excluded. The anti-arrhythmic medical product should be taken at least one hour before or three hours after CAESEVA, 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 CAESEVA. The phosphate serum level should be monitored and the CAESEVA 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

Sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, had no effect on the bioavailability of digoxin, warfarin, enalapril or metoprolol.

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 some reproductive toxicity when sevelamer was administered to rats at high doses (see section 5.3). Sevelamer has also been shown to reduce the absorption of several vitamins including folic acid (see sections 4.4 and 5.3). 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 foetus.

Breast-feeding
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 breast-feeding 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.

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 (≥ 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 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	Diarrhoea, dyspepsia, flatulence, abdominal pain		Intestinal obstruction, ileus/subileus, intestinal perforation ¹ , gastrointestinal haemorrhage ^{*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 4.4

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

4.9 Overdose
The symptoms observed in case of overdose are similar to adverse reactions listed in section 4.8, including mainly constipation and other known gastrointestinal disorders.

Appropriate symptomatic treatment should be provided.

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.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: All other therapeutic products, drugs for treatment of hyperkalemia and hyperphosphataemia. ATC code: V03A E02.

Mechanism of action
CAESEVA 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.

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.

5.2 Pharmacokinetic 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.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients

Tablet core:
Lactose monohydrate
Silica, colloidal
anhydrous Zinc stearate

Film-coating:
Opadry® 06A29148
Purified Water

6.2 Incompatibilities
Not applicable.

6.3 Shelf-life
3 years

6.4 Storage condition
Store below 30°C. Keep the container tightly closed in order to protect from moisture.

6.5 Nature and contents of container
HDPE bottles with a polypropylene cap containing 180 tablets per bottle.

7. MANUFACTURER
Synthon Hispania S.L.
C/Castello, 1 08830 Sant Boi de Llobregat (Barcelona) SPAIN

8. PRODUCT REGISTRATION HOLDER
Duopharma (M) Sdn Bhd
Lot 2599, Jalan Seruling 59, Kawasan 3, Taman Klang Jaya, 41200 Klang, Selangor Darul Ehsan.

9. DATE OF REVISION OF THE TEXT
June 2022

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