

# Sevela Film-Coated Tablet 800mg



## COMPOSITION

Each capsule contains:  
Sevelamer Carbonate 800mg

## Product Description

Off-white to white oval shaped film-coated tablet, "CH86" on single side.

## Pharmacodynamics

Pharmacotherapeutic group: All other therapeutic products, drugs for treatment of hyperkalemia and hyperphosphataemia. ATC code: V03AE02.

### Mechanism of action

Sevela 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.

## Pharmacokinetics

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.

In addition, the potential absorption and accumulation of sevelamer during long-term chronic treatment (> one year) cannot be totally excluded.

## Indication

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  $\geq 1.78$  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.

## Recommended Dose

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

Sevelamer carbonate should be given three times a day with meals.

### *Patients Not Taking a Phosphate Binder.*

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

*Table 1-Starting Dose for Patients Not Taking a Phosphate Binder*

| Serum Phosphorus             | Sevelamer carbonate 800mg             |
|------------------------------|---------------------------------------|
| >1.78 and <2.42 mmol/L       | 1 tablet three times daily with meals |
| $\geq 2.42$ and <2.91 mmol/L | 2 tablet three times daily with meals |
| $\geq 2.91$ mmol/L           | 2 tablet 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. The highest daily dose of sevelamer carbonate studied was 14 grams in CKD patients on dialysis.

### *Patients Switching from Calcium Acetate.*

In a study in 84 CKD patients on hemodialysis, a similar reduction in serum phosphorus was seen with equivalent doses (approximately mg for mg) of sevelamer hydrochloride and calcium acetate. Table 2 gives recommended starting doses of Sevelamer carbonate based on a patient's current calcium acetate dose.

*Table 2- Starting Dose for Dialysis Patients Switching from Calcium Acetate to Sevelamer carbonate*

| Calcium Acetate 667 mg (Tablets per meal) | Sevelamer carbonate 800mg (Tablets per meal) |
|-------------------------------------------|----------------------------------------------|
| 1 tablet                                  | 1 tablet                                     |
| 2 tablets                                 | 2 tablets                                    |
| 3 tablets                                 | 3 tablets                                    |

### *Dose Titration for All Patients Taking Sevelamer carbonate.*

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. Sevela should be taken with food and not on an empty stomach

## Contraindication

Sevelamer carbonate is contraindicated in patients with bowel obstruction.

Sevelamer carbonate is contraindicated in patients with known hypersensitivity to sevelamer carbonate, sevelamer hydrochloride, or to any of the excipients.

## Warning & 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 Sevela should only be initiated after careful benefit/risk assessment. If the therapy is initiated, patients suffering from these disorders should be monitored. Sevela treatment should be re-evaluated in patients who develop severe constipation or other severe gastrointestinal symptoms.

### Intestinal obstruction and ileus/subileus

Patients who are constipated should be monitored carefully while being treated with Sevela. 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.

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. Serum bicarbonate levels monitoring 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. 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

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 D<sub>3</sub> or one of its analogues to lower the intact parathyroid hormone (iPTH) levels.

### Inflammatory gastrointestinal disorders

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 maybe occurred. Inflammatory disorders may resolve upon sevelamer discontinuation. Sevelamer carbonate treatment should be re-evaluated in patients who develop severe gastrointestinal symptoms.

### Excipients

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

## Interactions With Other Medicaments

There are no empirical data on avoiding drug interactions between Sevelamer carbonate and most concomitant oral drugs. For oral medication where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy (e.g., cyclosporine, tacrolimus, levothyroxine), consider separation of the timing of the administration of the two drugs [see *Pharmacology*]. The duration of separation depends upon the absorption characteristics of the medication concomitantly administered, such as the time to reach peak systemic levels and whether the drug is an immediate release or an extended release product. Where possible consider monitoring clinical responses and/or blood levels of concomitant drugs that have a narrow therapeutic range.

*Table 4- Sevelamer Drug Interactions*

| <i>Oral drugs for which sevelamer did not alter the pharmacokinetics when administered concomitantly</i> |  |
|----------------------------------------------------------------------------------------------------------|--|
| Digoxin                                                                                                  |  |
| Enalapril                                                                                                |  |
| Iron                                                                                                     |  |
| Metoprolol                                                                                               |  |
| Warfarin                                                                                                 |  |

| <i>Oral drugs that have demonstrated interaction with sevelamer and are to be dosed separately from Sevelamer carbonate</i> |                                                                                          |
|-----------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| Ciprofloxacin                                                                                                               | <i>Dosing Recommendations</i><br>Take at least 2 hours before or 6 hours after sevelamer |
| Mycophenolate mofetil                                                                                                       | Take at least 2 hours before sevelamer                                                   |

Cyclosporin, mycophenolate mofetil and tacrolimus in transplant patients  
Reduced levels of cyclosporin, 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 cyclosporin, mycophenolate mofetil and tacrolimus should be considered during the use of combination and after its withdrawal

## Pregnancy & Lactation

### Pregnancy

There are no or limited amount of data from the use of sevelamer in pregnant women. 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.

### 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.

## Side Effects

### Summary of the safety profile

The most frequently occurring 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.

Adverse reactions that occurred are listed by frequency in the table below. The reporting rate is classified as very common, common, uncommon, rare, very rare, 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 <sup>1</sup> , gastrointestinal haemorrhage* <sup>1</sup> , intestinal ulceration* <sup>1</sup> , gastrointestinal necrosis* <sup>1</sup> , colitis* <sup>1</sup> , intestinal mass* <sup>1</sup> |
| Skin and subcutaneous tissue disorders |                                                      |                                                  |                   | Pruritus, rash                                                                                                                                                                                                                                                   |
| Investigations                         |                                                      |                                                  |                   | Crystal deposit intestine* <sup>1</sup>                                                                                                                                                                                                                          |

### \*post-marketing experience

<sup>1</sup> See inflammatory gastrointestinal disorders warning in section Warning & Precautions

### 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.

### **Symptoms & Treatment of Overdose**

In CKD patients on dialysis, the maximum dose studied was 14 grams of sevelamer carbonate and 13 grams of sevelamer hydrochloride. There are no reports of overdosage with sevelamer carbonate or sevelamer hydrochloride in patients. Since sevelamer is not absorbed, the risk of systemic toxicity is low.

### **Effects on Ability to Drive and Use Machine**

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

### **Packaging**

Available in 180 tablets/box

### **Storage Condition**

Store below 30°C and protect from light.

### **Manufacturer**

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### **Product Registration Holder**

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