13.2 Part VI.2 Elements for a Public Summary

13.2.1 Part VI.2.1 Overview of disease epidemiology

Hyperphosphatemia (increased levels of phosphorus in blood) and bone disease in patients with CKD (long-term kidney disease)

About 10% of European population is affected by CKD [ERA-EDTA, 2016] and 26 million American adults have CKD [Kidney, 2016].
Hyperphosphatemia is a major cause of death in patients with CKD. Studies showed increased risk for death with blood phosphate levels >3.5 mg/dL in CKD patients who were not on dialysis (process of purifying the blood in patients with kidney dysfunction) and 27% increase in risk of death with blood phosphorus >6.5 mg/dL among people receiving long term dialysis [Askar AM, 2015].
Bone and muscle pain, weakness and fractures of bone and sometimes avascular necrosis (death of bone tissue due to a lack of blood supply) can be seen in later stages of the disease. The incidence of bone fractures is very high in CKD patients. It is twice as high compared to patients without CKD. In severe forms of CKD osteoclastomas (brown tumors) can be seen [Pavlovic D, 2015].

13.2.2 Part VI.2.2 Summary of treatment benefits

In a systematic review and meta-analysis of 51 randomised trials comparing sevelamer or lanthanum with other phosphate binders in CKD, sevelamer was associated with a nonsignificant reduction in mortality and significantly lower hospitalisation rates and hypercalcaemia compared with calcium-based binders. The clinical relevance of these changes, however, is unknown since corresponding clinical outcomes were not reported [Habbous S, 2016].

A systematic review of 28 RCTs compared the effects of available phosphate binders on patient-important outcomes in patients with CKD-mineral and bone disorder. Higher mortality was observed with calcium than either sevelamer (moderate quality evidence) or non-calcium-based phosphate binders (NCBPBs; moderate quality evidence). Conventional meta-analysis suggested no difference in cardiovascular mortality between calcium and NCBPBs (low quality evidence) [Sekercioglu N, 2016].

In a cross-sectional, observational study in 151 haemodialysis-requiring ESRD patients, those patients receiving sevelamer showed significantly higher serum magnesium levels compared with those who did not, and a reduced risk of hypomagnesemia. A larger proportion of individuals receiving sevelamer were among those with normal serum magnesium, while among those with hypomagnesemia, a larger proportion were on proton pump inhibitors (PPIs). In the multivariate model including the use of PPIs, sevelamer carbonate resulted in an independent protective factor for hypomagnesemia [Rosa-Diez G, 2016].

A network meta-analysis of 77 randomised trials in CKD patients compared the effects of sevelamer, lanthanum, iron, calcium, colestilan, bixalomer, nicotinic acid and magnesium on

mortality. Compared to calcium, sevelamer reduced all-cause mortality, whereas treatment effects of lanthanum, iron, and colestilan were not significant. All phosphate binders lowered serum phosphorus levels to a greater extent than placebo, with iron ranked as the best treatment. Furthermore, sevelamer and lanthanum posed substantially lower risks for hypercalcaemia than calcium [Palmer SC, 2016].

A meta-analysis of 31 RCTs estimated the impact of sevelamer on cardiovascular calcification, cardiovascular mortality, all-cause mortality, and hospitalisation in patients on dialysis. Compared with calcium-based phosphate binders (CBPBs), sevelamer therapy resulted in smaller decreases in serum levels of phosphorus and a lower prevalence of hypercalcemia. A significant difference in coronary artery calcification scores and aortic calcification scores was observed between sevelamer and CBPBs. No significant difference was found in hospitalisation, all-cause mortality or cardiovascular mortality [Wang C, 2015].
A study was conducted in 79 patients undergoing hemodialysis (process of purifying blood through external filter in patients with kidney dysfunction) who first received sevelamer carbonate or sevelamer hydrochloride randomly for 8 weeks followed by a crossover (switch to the other treatment) for another 8 weeks. Both the drugs were found equivalent in controlling serum phosphorus. This study also suggested that sevelamer carbonate has advantages over sevelamer hydrochloride in the treatment of hyperphosphatemia in hemodialysis patients [Delmez J, 2007].

Similar study conducted in 31 patients undergoing hemodialysis who first received sevelamer carbonate powder or sevelamer hydrochloride tablets for 4 weeks followed by a crossover for another 4 weeks, demonstrated that both sevelamer carbonate powder and sevelamer hydrochloride tablets are equivalent in controlling serum phosphorus [Fan S, 2009].

Another study conducted over 8 weeks involving 49 patients with hyperphosphatemia (blood phosphorus level ≥5.5 mg/dl) who were not on hemodialysis suggested that sevelamer carbonate treatment resulted in significant reductions in serum phosphorus. The main measure of effectiveness was how much the blood phosphate was reduced at the end of the treatment. At least 70% of patients were able to achieve blood phosphorous within the ranges recommended for CKD patients [Ketteler M, 2008].

13.2.3 Part VI.2.3 Unknowns relating to treatment benefits

The efficacy of sevelamer carbonate has not been established in adult patients with CKD not on dialysis with serum phosphorus < 1.78 mmol/l. Therefore, sevelamer carbonate is currently not recommended for use in these patients.

The efficacy of sevelamer carbonate has not been established in children < 18 years.

The efficacy of sevelamer carbonate has not been established in patients with the following disorders:

- Dysphagia (difficulty or discomfort in swallowing)
- swallowing disorders

- severe gastrointestinal (organ system that extends from the mouth to the anus and carries out digestion of food) motility disorders including untreated or severe gastroparesis (condition in which your stomach cannot empty itself of food due to nerve damage), retention of gastric contents and abnormal or irregular bowel motion
- inflammatory bowel disease
- major gastrointestinal tract surgery

Therefore, caution should be exercised when sevelamer carbonate is used in these patients.

13.2.4 Part VI.2.4 Summary of safety concerns

Table 13-5 Important identified risks

Risk	What is known	Preventability
A hole in the wall of gut, obstruction in the gut and lack of movement in the intestines that leads to a buildup or blockage of food material (Intestinal perforation, obstruction and ileus)	The safety and efficacy of sevelamer carbonate have not been established in patients with severe disorders of obstruction and inflammation of gut. Constipation and upper abdominal pain are very common side effects (more than 1 in 10 people) and abdominal pain, indigestion and flatulence are common side effects (1 in 10 people) of sevelamer carbonate. In clinical use, cases of slow intestine motility/blockages in the intestine and perforation in the intestine wall have been reported.	Caution should be exercised when sevelamer carbonate is used in patients with severe disorders of obstruction and inflammation of gut. Since constipation may be an early symptom of a blockage in intestine, patients should inform their doctor or pharmacist if they experience constipation. Patients on peritoneal dialysis should inform their doctor immediately if they experience any new signs or symptoms of abdominal distress, abdominal swelling, abdominal pain, abdominal tenderness, or abdominal rigidity or constipation. They should be monitored more carefully for problems with low levels of vitamins A, D, E, K and folic acid.

Table 13-6 Important potential risks

Risk	What is known
Serious drug induced gastrointestinal system disorders due to the use of sevelamer crystals (Serious gastrointestinal disorders associated with sevelamer crystals)	Patient is advised not to take sevelamer carbonate if he/she is suffering from bowel obstruction (blockage of either small gut or large gut that results in prevention of the normal movement of the products of digestion). Before taking sevelamer carbonate, patient should inform the doctor if suffering from any of the following problems: • swallowing problems

Risk	What is known
	• problems with motility (movement) in the stomach and bowel • being sick frequently • active inflammation of the bowel • have undergone major surgery on the stomach or bowel. Patient might develop peritonitis (infection of the abdominal fluid) that is associated with peritoneal dialysis (process of removal of waste products through peritoneum, the inside lining of belly that acts as a natural filter for blood in patients with kidney dysfunction). This risk can be reduced by carefully following the sterile techniques to prevent contamination from microorganisms during bag changes. Patient should inform the doctor immediately if he/she experiences any new signs or symptoms of abdominal distress, abdominal swelling, abdominal pain, abdominal tenderness, or abdominal stiffness, constipation (a condition in which there is difficulty in emptying the bowels, usually associated with hardened feces), fever, chills, nausea or vomiting. Vomiting, constipation, upper abdominal pain, and nausea are very common side effect (more than 1 in 10 people); diarrhea, abdominal pain, indigestion and flatulence (excessive stomach and/or intestinal gas) are common side effects (1 in 10 people) observed under the therapy with sevelamer carbonate. In clinical use, slow bowel movement, blockages of the intestine or whole formation in the wall of the intestine have been reported. Patient should inform the doctor or pharmacist if suffering from constipation as it might be an early symptom for blockage of intestine.
Allergic reactions including swelling beneath the surface of the skin and an serious life-threatening allergic reaction in patients treated with sevelamer carbonate (Hypersensitivity reactions, including angioedema and anaphylactic reactions in patients treated with sevelamer carbonate)	Patient is advised not to take sevelamer carbonate if allergic to the active substance or to any of the other ingredients of this medicine. In clinical use, cases of itching and rash have been reported.
Difficulty swallowing tablets	Before taking sevelamer carbonate, patient should inform the doctor if suffering from any swallowing problems such as difficulty or discomfort in swallowing. Therefore, caution should be advised in such patients when using sevelamer carbonate. The tablets must be swallowed whole and is not supposed to be crushed, chewed or break into pieces.

Risk	What is known
	For patients with swallowing difficulties, sevelamer carbonate is also available as a powder for oral suspension.
Drug induced low vitamin levels in the body (Vitamin deficiency)	Sevelamer has also been shown to reduce the absorption of several vitamins including folic acid. It also binds with bile acids and thus interferes with the absorption of fat soluble vitamins such as A, D, E and K (a water soluble vitamin that helps the body to produce and maintain new cells, and also helps prevent changes to DNA that may lead to cancer). Due to either kidney condition or dialysis treatment, the patient might develop: • Low amount of vitamin D in blood. Therefore, the doctor will monitor the levels of vitamin D in the blood and prescribe additional vitamin D as necessary. If the patient does not take multivitamin supplements, he/she might develop low levels of vitamins A, E, K and folic acid in the blood and therefore doctor may monitor these levels and prescribe supplemental vitamins as necessary. There are no data from the use of sevelamer in pregnant women. Sevelamer carbonate has also been shown to reduce the absorption of several vitamins including folic acid.
Interaction of sevelamer carbonate with medicines used to treatment low thyroid hormone levels (levothyroxine); antibiotics, medicines used to suppress the immune system (immunosuppressants); medicines to treat heart rhythm problems (antiarrythmics), for epilepsy (anticonvulsants); and medicines that are used to treat fungal (including yeast) infections (antifungal drugs) (Drug interaction with levothyroxine, ciprofloxacin, immunosuppressants, antiarrythmics, anticonvulsants and antifungal drugs)	Doctor should be informed if the patient is taking or have recently taken or might take any other medicines. Thyroid hormone deficiency may uncommonly be observed in certain people taking levothyroxine and sevelamer carbonate. Therefore, the doctor may monitor the levels of TSH in the patient's blood more closely. Sevelamer carbonate should not be taken at the same time as ciprofloxacin (an antibiotic). Doctor should advise the patients before taking medicines such as ciclosporin, mycophenolate mofetil and tacrolimus (medicines used to suppress the immune system) as their effect might be reduced by sevelamer carbonate. Patient should consult the doctor before taking any medicines for heart rhythm problems or for epilepsy.
Use of sevelamer carbonate for diseases not intended to be treated with that drug in patients < 18 years of age (Off label use in patients <18 year-old)	The safety and efficacy in children (below the age of 18 years) has not been established. Therefore sevelamer carbonate is not recommended for use in children. This medicine should be kept out of the sight and reach of children.

Table 13-7 Missing information

Risk	What is known

Risk	What is known
Use in pregnancy and breast feeding (Use in pregnancy and lactation)	If patients are pregnant or breast-feeding, think they might be pregnant or are planning to have a baby, they should talk to their doctor for advice before taking this medicine. It is unknown whether sevelamer carbonate has any effect on unborn babies. Patients should inform their doctor if they wish to breast-feed their baby. It is unknown whether sevelamer carbonate may pass through breast milk and affect baby. Patients should consult their doctor or pharmacist for advice before taking any medicine.
Use in liver dysfunction and in patients with lowered immunity (Use in hepatic impairment and in immunocompromised patients)	Currently no adequate data are available about the use of sevelamer carbonate in hepatic impairment and in immunocompromised patients.

13.2.5 Part VI.2.5 Summary of additional risk minimization measures by safety concern

All medicines have a SmPC which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimizing them. An abbreviated version of this in lay language is provided in the form of the package leaflet. The measures in these documents are known as routine risk minimization measures.

This medicine has no additional risk minimization measures.

13.2.6 Part VI.2.6 Planned post authorization development plan

None

13.2.7 Part VI.2.7 Summary of changes to the Risk Management Plan over time

N/A, this is the first Sandoz RMP for the product.