VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Long term (chronic) kidney disease (CKD) has become a major worldwide healthcare problem, affecting an estimated 5%–10% of the world's population (1).

Patients with CKD cannot eliminate phosphate from their bodies. This leads to hyperphosphataemia (high blood phosphate levels), which, in the long term, can cause complications such as heart disease. The active substance sevelamer carbonate is a phosphate binder. When taken with meals, sevelamer carbonate binds to phosphate from food within the gut, preventing it from being absorbed into the body. This helps to reduce the phosphate levels in the blood.

Sevelamer carbonate is used to control hyperphosphataemia in:

• Adult patients on dialysis (a blood clearance technique). It can be used in patients undergoing haemodialysis (using a blood filtration machine) or peritoneal dialysis (where fluid is pumped into the abdomen and an internal body membrane filters the blood).

• Patients with CKD who are not on dialysis and have a blood phosphorus level ≥1.78 mmol/L (7, 52).

Sevelamer carbonate should be used with other treatments such as calcium supplements and vitamin D supplements to prevent the development of bone disease (52).

VI.2.2 Summary of treatment benefits

Two main studies compared Renvela (sevelamer carbonate) with Renagel (sevelamer hydrochloride) in 110 adults who were on dialysis. All patients had CKD with hyperphosphatemia and had been on haemodialysis for at least three months. They had all previously received oral phosphate binder treatment and most patients took vitamin D. The two studies were crossover studies: patients first received either Renvela or Renagel (tablets, 79 patients, or powder, 31 patients), and the treatments were then switched after four or eight weeks. The main measure of effectiveness was the average amount of phosphate in the blood during treatment. Renvela was as effective as Renagel in reducing phosphate in the studied patients. The average amount of phosphate in the blood during treatments with Renvela or Renagel was similar (52).

A third main study involving 49 patients studied Renvela in patients with hyperphosphatemia with a serum phosphorus level equal to or above 1.78 mmol/L and who were not on dialysis. Patients received Renvela for eight weeks. The main measure of effectiveness was how much the blood phosphate was reduced at the end of the treatment. In this study, the average amount of phosphate in the blood was reduced by about a fifth, from 2.0 mmol/L to 1.6 mmol/L (52).

These studies were conducted for reference products Renvela and Renagel by Genzyme and not by Mylan.

VI.2.3 Unknowns relating to treatment benefits

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

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

Use in pregnancy and lactation

It is unknown whether sevelamer carbonate has any effect on unborn babies. It is unknown whether sevelamer carbonate may pass through breast milk and affect the baby.

Use in hepatic impairment and in immunocompromised patients

The safety and efficacy of sevelamer carbonate has not been established in adult patients with hepatic impairment (namely chronic kidney disease not on dialysis with serum phosphorus < 1.78 mmol/l) and in immunocompromised patients.

Driving and using machines

No studies on the effects on the ability to drive and use machines have been performed. Patients on sevelamer should not drive or use any tools or machines.

Patients <18 year-old

Patients who were less than 18 years of age were excluded from the clinical trial programme. Hence, the safety and efficacy of sevelamer hydrochloride in this patient population is unknown.

VI.2.4 Summary of safety concerns

Table 33 Part VI - Summary table of safety concerns

Important identified risks

Risk	What is known	Preventability
Blockages in the intestine and perforations in the intestine wall (Intestinal perforation, obstruction and ileus)	Blockages in the intestine and perforations in the intestine wall have been previously associated with sevelamer.	Yes, by identifying those at risk, minimizing the risks and monitoring for early symptoms. Patients are advised not to take sevelamer carbonate in case they have bowel obstruction as well as to inform their doctor or pharmacist in case they experience constipation, which may be an early symptom of intestinal blockage.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Allergic reactions to drug (Hypersensitivity reactions, including angioedema and anaphylactic reactions)	Patients may develop itching and rash suggestive of allergic reaction to the drug. Patients are advised not to take sevelamer carbonate in case they are allergic to the active substance or to any of the other ingredients of this medicine.
Difficulty swallowing tablets	There have been reports of difficulty swallowing sevelamer tablets. Many of these cases involved patients with simultaneous medical conditions including swallowing disorders or abnormalities in the foodpipe (esophagus).
Vitamin deficiency	Depending on dietary intake and the severity of their disease, patients with long-lasting kidney disease (chronic kidney disease) may develop low levels of vitamins A, D, E and K.
Drug interactions with ciprofloxacin (antibiotic), levothyroxine (used to treatment low thyroid hormone levels), medicines for heart rhythm problems, for epilepsy and antifungal drugs (Drug interactions with ciprofloxacin, levothyroxine, antiarrhythmics, anticonvulsants and antifungal drugs)	Data from clinical studies have shown that sevelamer can affect the effects of medicines such as ciproftoxacin, ciclosporin, mycophenolate mofetil, levothyroxine and tacrolimus. Sevelamer carbonate should not be taken at the same time as ciprofloxacin (an antibiotic). If taking medicines for heart rhythm problems or for epilepsy, the doctor should be consulted when taking sevelamer carbonate. The effects of medicines such as ciclosporin, mycophenolate mofetil and tacrolimus (medicines used to suppress the immune system) may be reduced by sevelamer carbonate. Thyroid hormone deficiency may uncommonly be observed in certain people taking levothyroxine (used to treat low thyroid hormone levels) and sevelamer carbonate. In case sevelamer carbonate is to be taken at the same time as another medicine, patients' physician may advise them to take this medicine 1 hour before or 3 hours after sevelamer, or they may consider monitoring the blood levels of that other medicine.

Risk	What is known (Including reason why it is considered a potential risk)
Off-label use in children (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 is not recommended for use in children.

Missing information

Risk	What is known
Use in pregnancy and lactation	It is unknown whether sevelamer has any effect on unborn babies. Sevelamer 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. It is also unknown whether sevelamer may pass through breast milk and affect the baby. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with sevelamer should be made taking into account the benefit of breast-feeding to the child and the benefit of sevelamer therapy to the woman.
Use in hepatic impairment and in immunocompromised patients	Clinical trials excluded those patients with Human Immunodeficiency Virus, patients with an impaired immune system and patients with liver impairment.

VI.2.5 Summary of risk minimisation measures by safety concern

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

The SPC and the PL for sevelamer carbonate can be found in the sevelamer carbonate's EPAR page.

VI.2.6 Planned post authorisation development plan

No studies planned.

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

Version	Date	Safety Concerns	Comment
Version 4.0	16-Mar-2016	The following safety concerns were added in the sequence depicted below. Important identified risks: intestinal perforation, obstruction and ileus; Important potential risks: hypersensitivity reactions, including angioedema and anaphylactic reactions, difficulty swallowing tablets, drug interactions with ciprofloxacin, levothyroxine, antiarrhythimic, anticonvulsants and antifungal drugs;	This RMP was updated from version RMP.NUS.25293 (3.0) to version 4.0 in line with the Company RMP template, the 01-04 Dec 2014 PRAC meeting minutes, the RMS DK during the RUP and the current Innovator's RMP for Renvela.

Version	Date	Safety Concerns	Comment
		Missing information: use in hepatic impairment and in immunocompromised patients.	