## 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[30].

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[17,18].

Sevelamer carbonate should be used with other treatments such as calcium supplements and vitamin D supplements to prevent the development of bone disease[17].

### 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 hyperphosphataemia and had been on haemodialyis 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[17].

A third main study involving 49 patients studied Renvela® in patients with hyperphosphataemia 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[17].

### VI.2.3 Unknowns relating to treatment benefits

The safety and efficacy of sevelamer carbonate have not been established in patients with liver damage and a less efficient immune system. Therefore caution should be exercised when sevelamer carbonate is used in these patients. In addition, there is not enough information on the use of sevelamer in women who are pregnant or breast-feeding. It is unknown whether sevelamer carbonate has any effect on unborn babies and whether sevelamer carbonate passes through breast milk.

### VI.2.4 Summary of safety concerns

The most common side effects with sevelamer carbonate (seen in more than one patient in 10) are nausea (feeling sick), vomiting, upper abdominal (tummy) pain and constipation. For the full list of all side effects reported with sevelamer, see the Package Leaflet[17].
Sevelamer carbonate should not be used in people who may be hypersensitive (allergic) to sevelamer carbonate or any of the other ingredients. Sevelamer must not be used in people with hyperphosphataemia (low blood phosphate levels) or with bowel obstruction (a blockage in the gut)[17].

The Table 5 summarizes what is known about each important identified risk associated with the use of sevelamer carbonate and its preventability. Current knowledge on important potential risks and missing information associated with the use of sevelamer carbonate is summarized in Table 6 and **Error! Reference source not found.**, respectively.

**Table 5. Important identified risks related to the use of sevelamer carbonate, and their preventability**

| Important identified risks | What is known | Preventability |
|---|---|---|
| Intestinal perforation, blockages in the intestine and absence of the normal contractile movements of the intestine wall (ileus) | It occurs with an unknown frequency. | Intestinal blockages can be prevented by informing the physician on signs of constipation. If the patient develops signs of intestinal perforation such as nausea, vomiting, and loss of appetite (anorexia), the patient should inform the physician. |

**Table 6. Important potential risks related to the use of sevelamer carbonate.**

| Important potential risks | What is known |
|---|---|
| Serious disorders of different parts of the digestive (gastrointestinal) system associated with sevelamer crystals | Cases of serious disorders of different parts of the digestive system (*e.g.* bleeding, perforation, bloody diarrhoea, death of tissue lining the intestine wall) associated with the presence of sevelamer crystals have been reported. However, it has not been demonstrated yet that sevelamer causes such disorders. |
| Allergic reactions (Hypersensitivity reactions) | Sevelamer carbonate or any of the other ingredients of this product may cause allergic reactions, such as rapid swelling of the skin (angioedema) or other sudden, widespread, potentially life-threatening allergic reactions (anaphylactic reactions). Sevelamer carbonate should not be used in patients who may be allergic (hypersensitive) to sevelamer carbonate or any of the other ingredients of this product. |
| Swallowing problems | It is an uncommon adverse event (affects 1 user in 1000). Many of these case reports collected involved patients with co-morbid conditions including swallowing disorders or oesophageal abnormalities. |
| Vitamin deficiency | A low amount of vitamin D in the blood may develop due to either the kidney condition or the dialysis treatment. It cannot be excluded that sevelamer carbonate binds to fat-soluble vitamins contained in ingested food and therefore impair their absorption. |

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|---|---|
| Interaction with other medicines (*e.g.* ciprofloxacin, levothyroxine, antiarrythmics, anticonvulsants antifungal drugs, andimmunosuppressants) | Sevelamer carbonate should not be taken at the same time as ciprofloxacin (an antibiotic).<br>If the patient is taking medicines for heart rhythm problems (anti-arrhythmics) or for epilepsy (anti-convulsants), the physician should be consulted when taking sevelamer carbonate.<br>The effects of medicines used to suppress the immune system such as ciclosporin, mycophenolate mofetil and tacrolimus (immunosuppressants) may be reduced by sevelamer carbonate.<br>Thyroid hormone deficiency may uncommonly be observed in certain people taking levothyroxine (used to treat low thyroid hormone levels) and sevelamer carbonate. |
| Off- label use in patients below the age of 18 years | 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. |

**Table 7. Missing information on the use of sevelamer carbonate.**

| Missing information | What is known |
|---|---|
| Pregnancy and breast-feeding | It is unknown whether sevelamer carbonate has any harmful effect on unborn babies.<br>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.<br>It is unknown whether sevelamer carbonate may pass through breast milk and affect the baby.<br>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 mother. |
| Liver damage in patients with a less efficient immune system | Studies have not been performed. Sevelamer is not absorbed. Therefore, it is not expected to cause liver toxicity. |

### VI.2.5 Summary table of risk minimization activities by safety concern

All medicines have a Summary of Product Characteristics (SmPC) 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 SmPC and the PL for sevelamer carbonate can be found on the sevelamer carbonate's EPAR page.

### VI.2.6 Planned post-authorisation development plan

No post-authorization development is planned for Sevelamer carbonate 800 mg film-coated tablets.

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

Major changes to the Risk Management Plan over time

| Version | Date | Safety Concerns | Comment |
|---|---|---|---|
| 5 | < enter date> | Addition of the following safety concerns:<br>- Important identified risk: "Intestinal perforation";<br>- Important potential risk: "Serious gastrointestinal disorders associated with sevelamer crystals", "Hypersensitivity reactions, including angioedema and anaphylactic reactions", "Difficulty swallowing tablets", "Drug interactions with levothyroxine, ciprofloxacin, immunosuppressants, antiarrythmics, anticonvulsants and antifungal drugs";<br>- Missing information: "Use in hepatic impairment and in immunocompromised patients".<br><br>Removal of additional risk minimisation measures and educational materials related to:<br>- the risk factors for and prevention of peritonitis | - Safety concerns have been added based on the Pharmacovigilance Risk Assessment Committee (PRAC) assessment report of the Periodic Safety Update Report for sevelamer: (Procedure no.: EMEA/H/C/PSUSA/00002697/20151) [21]<br><br>- Risk minimisation measures and educational materials have been removed based on the requirement of the Belgium authorities [24].<br><br>Update according to Marketing authorisation transfer |

| Version | Date | Safety Concerns | Comment |
|---|---|---|---|
| | | in peritoneal dialysis patients;<br>- the risk factors for and prevention of AV fistula site complications in haemodialysis patients;<br>- the increased risk of vitamin deficiency in chronic kidney disease patients and the need for vitamin supplementation. | |