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[32].

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[19,20].

Sevelamer carbonate should be used with other treatments such as calcium supplements and vitamin D supplements to prevent the development of bone disease[19].

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[19].

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[19].

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.

Hyperphosphataemic CKD patients not on dialysis with serum phosphorus <1.78 mmol/L
The safety and efficacy of sevelamer carbonate have 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.

Hyperphosphataemic CKD patients on peritoneal dialysis
Patients on peritoneal dialysis, in particular, may develop peritonitis (infection of the abdominal fluid). These patients should expect to be monitored more carefully for problems with low levels of vitamins A, D, E, K and folic acid, since this was not measured in a clinical study in these patients.

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

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.

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[19].
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)[19].

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 Table 7, respectively.

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

Important identified risks	What is known	Preventability
Increased thyroid stimulating hormone levels/ Hypothyroidism	Thyroid hormone deficiency may uncommonly be observed in certain people taking levothyroxine (used to treat low thyroid hormone levels) and sevelamer carbonate.	It can be prevented by monitoring the levels of thyroid stimulating hormone in the blood more closely.
Intestinal obstruction/ileus	It is a very rare adverse event (affects one user in 10,000).	It can be prevented by informing the physician on signs of constipation.

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

Important potential risks	What is known
Arterio-venous (AV) fistula complications (in haemodialysis patients)	An AV fistula is an artificial connection between an artery and a vein. It is created by a surgeon. AV fistula operation and AV fistula complication were observed among the common all causality AEs during sevelamer treatment[18].
Interaction with other medicines (*e.g.* ciprofloxacin, ciclosporin, levothyroxine, mycophenolate mofetil, 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.
Swallowing problems (Dysphagia)	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.

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.
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
Infection of the abdominal fluid (Peritonitis)	Peritonitis may develop associated with peritoneal dialysis.
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.

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

Missing information	What is known
CKD patients not on dialysis with high levels of phosphate in the blood (hyperphosphataemia), but still lower than 1.78 mmol/L	A main study involving 49 patients studied Renvela® in patients with hyperphosphataemia with a serum phosphorus level higher than or equal to 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[19]. However, the safety and efficacy of sevelamer carbonate have not been established in adult patients with CKD not on dialysis with blood phosphate level lower than 1.78 mmol/L. Therefore sevelamer carbonate is currently not recommended for use in these patients.
Hyperphosphataemic CKD patients on peritoneal dialysis	Two main studies compared Renvela® (sevelamer carbonate) with Renagel® (sevelamer hydrochloride) in 110 adults who were on dialysis. All patients had chronic kidney disease 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[19]. Patients on peritoneal dialysis, in particular, may develop peritonitis (infection of the abdominal fluid). This risk can be reduced by careful adherence to sterile techniques during bag changes. Patients should tell their doctor immediately if they experience any new signs or symptoms of abdominal distress, abdominal swelling, abdominal pain, abdominal tenderness, or abdominal rigidity, constipation, fever, chills, nausea or vomiting. These patients should expect to be monitored more carefully for problems with low levels of vitamins A, D, E, K and folic acid[22].

Pregnancy and breast-feeding	It is unknown whether sevelamer carbonate has any affect 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 unknown whether sevelamer carbonate 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.

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 in the sevelamer carbonate's EPAR page.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). Full details on these conditions and the key elements of any educational material can be found in Annex II of the product information which is published in sevelamer carbonate's EPAR page; how they are implemented in each country, however, will depend upon agreement between the manufacturer and the national authorities.

These additional risk minimisation measures are for the following risks:

Risk	Risk minimisation measure
AV fistula(*) complications (in haemodialysis patients)	Educational material on risk factors for AV fistula site complications and their prevention in haemodialysis patients
Infection of the abdominal fluid (Peritonitis)	Educational material on risk factors for peritonitis and its prevention in peritoneal dialysis patients.
Vitamin deficiency	Educational material on the increased risk of vitamin deficiency in chronic kidney disease patients being prescribed sevelamer.

(*) An AV fistula is an artificial connection between an artery and a vein. It is created by a surgeon.

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

Not applicable.