Approved Professional Information for RENVELA TABLETS

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

RENVELA® TABLETS 800 mg film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains 800 mg of sevelamer carbonate on an anhydrous basis.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablets.

White to off-white oval tablet, printed with “RENVELA 800” on crown, single side, in black ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

RENVELA TABLETS are indicated for the control of hyperphosphataemia in adult patients receiving haemodialysis or peritoneal dialysis and adult chronic kidney disease (CKD) patients not on dialysis with serum phosphorus > 1,78 mmol/L.

4.2 Posology and method of administration

Posology

Initial dose

The recommended starting dose is 2,4 g to 4,8 g per day based on clinical needs and phosphorus level.

RENVELA TABLETS must be taken three times per day with meals.

For patients previously on phosphate binders, RENVELA TABLETS should be given on a gram for gram basis with monitoring of serum phosphorus levels to ensure optimal daily doses.

Titration and maintenance

Serum phosphorus levels must be monitored and the dose of RENVELA TABLETS titrated every 2 – 4 weeks until an acceptable serum phosphorus level is reached, with regular monitoring thereafter.

Patients taking RENVELA TABLETS should adhere to their prescribed diets. In clinical practice, treatment will be continuous based on the need to control serum phosphorus levels and the daily dose is expected to be an average of approximately 6 g per day.

Special populations

Paediatric population

The safety and efficacy of RENVELA TABLETS have not been established in children below the age of 18 years. RENVELA TABLETS is not recommended for use in children below the age of 18 years.

Elderly population

There is no evidence for special considerations when RENVELA TABLETS is administered to elderly patients.

Hepatic impairment

No studies have been performed in patients with hepatic impairment.

Method of administration

Oral use.

RENVELA tablets (800 mg) can be taken three times per day with meals at a dosage based on individual patient requirements to control phosphate levels.

The tablets should be swallowed intact and should not be crushed, chewed, or broken into pieces prior to administration.

4.3 Contraindications

- Hypersensitivity to sevelamer carbonate or any other ingredients of RENVELA TABLETS (see section 6.1).
- Patients with hypophosphataemia or bowel obstruction.

4.4 Special warnings and precautions for use

The safety and efficacy of RENVELA TABLETS in patients with dysphagia, swallowing disorders, severe gastrointestinal motility disorders, including severe constipation, untreated or severe gastroparesis, retention of gastric contents and abnormal or irregular bowel motion, active inflammatory bowel disease or major gastrointestinal tract surgery, have not been established. Consequently, caution should be exercised when RENVELA TABLETS is used in patients with these disorders. RENVELA TABLETS treatment should be re-evaluated in patients who develop severe constipation or other severe gastrointestinal symptoms.

Swallowing and choking difficulties

Case reports of difficulty swallowing the tablet have been reported. Many of these cases involved patients with contributing co-morbid conditions affecting the ability to swallow, including swallowing disorders or oesophageal abnormalities. Proper swallowing ability should be carefully monitored in patients with co-morbid conditions. Caution should be exercised when RENVELA TABLETS are used in these patients.

Fat-soluble vitamins and folate deficiency

Patients with CKD may develop low vitamin A, D, E and K levels, depending on dietary intake and the severity of their disease. Treatment with sevelamer in preclinical studies has been shown to reduce the absorption of vitamins D, E and K and folic acid. Therefore, in patients not taking supplemental vitamins but on RENVELA TABLETS, serum vitamin A, D and E levels, and vitamin 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 RENVELA TABLETS. In patients undergoing peritoneal dialysis additional monitoring of fat-soluble vitamins and folic acid is recommended, since vitamin A, D, E and K levels were not measured in a clinical study in these patients.

There is at present insufficient data to exclude the possibility of folate deficiency during long term RENVELA TABLETS treatment. In patients not taking supplemental folic acid but on RENVELA TABLETS, folate level should be assessed regularly.

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 and in a clinical trial with sevelamer hydrochloride, a greater number of peritonitis cases were reported in the sevelamer group than in the control group. 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.

Hypothyroidism

Closer monitoring of patients with hypothyroidism co-administered with RENVELA TABLETS and levothyroxine is recommended (see section 4.5).

Inflammatory gastrointestinal disorders

Cases of serious inflammatory disorders of the gastrointestinal tract (complications including haemorrhage, perforation, ulceration, necrosis, colitis, and colonic/caecal mass) associated with the presence of sevelamer crystals have been reported (see section 4.8). Inflammatory disorders may resolve upon RENVELA TABLETS discontinuation. Treatment with RENVELA TABLETS should be re-evaluated in patients who develop severe gastrointestinal symptoms.

Excipients

RENVELA TABLETS contains less than 1 mmol sodium (23 mg) per tablet that is to say essentially "sodium-free".

4.5 Interaction with other medicines and other forms of interaction

RENVELA has been studied in two medicine interaction studies. In interaction studies in healthy volunteers, sevelamer carbonate did not affect the bioavailability of either warfarin or digoxin.

Sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate (RENVELA TABLETS), has been studied in medicine interaction studies. In interaction studies in healthy volunteers, sevelamer hydrochloride had no effect on the bioavailability of a single dose of digoxin, warfarin, enalapril, metoprolol or iron. However, the bioavailability of ciprofloxacin was decreased by approximately 50 % when co-administered with sevelamer hydrochloride in a single dose study. Consequently, sevelamer hydrochloride, and thus RENVELA TABLETS (sevelamer carbonate), should not be taken simultaneously with ciprofloxacin.

During post-marketing experience, reduced concentrations of ciclosporin, mycophenolate mofetil and tacrolimus have been reported in transplant patients when co-administered with sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, without any clinical consequences (for example, graft rejection). The possibility of an interaction cannot be

excluded and close monitoring of blood concentrations of ciclosporin, mycophenolate mofetil and tacrolimus should be considered during the use of any of these medicines with RENVELA TABLETS and after its withdrawal.

During post-marketing experience, cases of increased thyroid stimulating hormone (TSH) levels have been reported in patients co-administered sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, and levothyroxine. Closer monitoring of TSH levels is therefore recommended in patients receiving RENVELA TABLETS and levothyroxine.

During post-marketing experience, cases of increased phosphate levels have been reported in patients taking proton pump inhibitors co-administered with sevelamer carbonate. Caution should be exercised when prescribing proton pump inhibitors to patients concomitantly treated with RENVELA TABLETS. The phosphate serum level should be monitored and the RENVELA TABLETS dosage adjusted consequently.

Sevelamer carbonate is not absorbed and may affect the bioavailability of other medicines. When administering an oral medicine where a reduction in the bioavailability of that medicine would have a clinically significant effect on its safety or efficacy, the medicine should be administered at least one hour before or three hours after taking RENVELA TABLETS, or the medical practitioner should consider monitoring blood levels of the medicine. Patients taking antidysrhythmic medicines for the control of dysrhythmias and anti-seizure medicines for the control of seizure disorders, were excluded from the clinical trials. Special precautions should be taken when prescribing RENVELA TABLETS to patients also taking these medicines. Possible reduction in absorption cannot be excluded. The antidysrhythmic medicine should be taken at least one hour before or three hours after RENVELA TABLETS, and blood monitoring can be considered.

4.6 Fertility, pregnancy and lactation

The safety of RENVELA TABLETS has not been established in pregnant or lactating women.

Since sevelamer is not absorbed, excretion in breast milk is not expected.

A decision on whether to continue/discontinue breastfeeding or to continue/discontinue therapy with RENVELA TABLETS should be made taking into account the benefit of breastfeeding to the child and the benefit of RENVELA TABLETS therapy to the woman.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive a vehicle and use machines have been performed.

4.8 Undesirable effects

The safety of sevelamer (as either carbonate and hydrochloride salts) has been investigated in numerous clinical trials involving a total of 969 haemodialysis patients with treatment duration of 4 to 50 weeks (724 patients treated with sevelamer hydrochloride and 245 with sevelamer carbonate), 97 peritoneal dialysis patients with treatment duration of 12 weeks (all treated with sevelamer hydrochloride) and 128 patients with CKD not on dialysis with treatment duration of 8 to 12 weeks (79 patients treated with sevelamer hydrochloride and 49 with sevelamer carbonate).

In a parallel study with a treatment duration of 12 weeks, the adverse events reported for sevelamer hydrochloride in peritoneal dialysis patients (N = 97) were similar to adverse events observed in haemodialysis patients.

In a double-blind, placebo-controlled, dose titration study with a treatment duration of 8 weeks,

the adverse events experienced by the patients in the sevelamer carbonate and placebo groups were similar.

The most frequently occurring (≥ 5 % of patients) undesirable effects possibly or probably related to sevelamer, including RENVELA TABLETS, were in the gastrointestinal disorders system organ class. Most of these adverse reactions were mild to moderate in intensity.

The reporting rate is classified as very common (≥ 1/10), common (≥ 1/100 to < 1/10).

MedDRA system organ class	Very common	Common
Gastrointestinal disorders	Nausea, vomiting, upper abdominal pain, constipation, diarrhoea, dyspepsia	Flatulence, abdominal pain, abdominal distension, anorexia, abdominal discomfort
Skin and subcutaneous tissue disorders		Pruritus
General disorders and administration site conditions		Fatigue

Post-marketing experience:

MedDRA system organ class	Frequency unknown
Immune system disorders	Hypersensitivity
Gastrointestinal disorders	Ileus, intestinal obstruction, intestinal perforation. Cases of serious inflammatory disorders of the gastrointestinal tract (with complications including haemorrhage, perforation, ulceration, necrosis, colitis and intestinal mass) associated with the presence of sevelamer crystals.
Skin and subcutaneous tissue disorders	Rash

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of RENVELA TABLETS is important. It allows continued monitoring of the benefit/risk balance of RENVELA TABLETS. Health care providers are asked to report any suspected adverse reactions to:

- The Pharmacovigilance Unit at Sanofi: za.drugsafety@sanofi.com (email) or 011 256 3700 (tel), or
- SAHPRA via the "**Adverse Drug Reactions Reporting Form**" found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

In CKD patients on dialysis, the maximum dose studied was 14,4 grams of sevelamer carbonate. There are no reports of overdosage with sevelamer carbonate in patients. Sevelamer is not systemically absorbed, the risk of systemic toxicity is low. Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: All other therapeutic products, medicines for treatment of hyperkalaemia and hyperphosphataemia.

ATC code: V03A E02.

Category and class: A 32.16 Others.

5.1 Pharmacodynamic properties

Sevelamer carbonate is a non-absorbed phosphate binding cross-linked polymer, free of metal and calcium.

It contains multiple amines separated by one carbon from the polymer backbone. These amines exist in a protonated form in the intestine and interact with phosphate molecules through ionic and hydrogen bonding. By binding phosphate in the dietary tract and decreasing absorption, sevelamer carbonate lowers the phosphate concentration in the serum.

In addition to effects on serum phosphate levels, sevelamer hydrochloride has been shown to bind bile acids in vitro and in vivo in experimental animal models. Because sevelamer binds bile acids, it may interfere with normal fat absorption and thus may reduce absorption of fat soluble vitamins such as A, D and K. Mean LDL cholesterol and mean total cholesterol declined significantly on sevelamer treatment (-39 % and -21 %, respectively). This effect is observed after 2 weeks. Triglycerides, HDL cholesterol and albumin did not change.

5.2 Pharmacokinetic properties

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, as confirmed by an absorption study in healthy volunteers.

5.3 Preclinical safety data

No further information of relevance available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Microcrystalline cellulose

Sodium chloride

Zinc stearate

Film coating:

Opadry Clear containing:

Diacetylated monoglycerides

Hypromellose (E464)

Printing ink:

Opacode Black ink containing:

Hypromellose

Black iron oxide (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C. Protect from moisture.

Keep tablets in the bottle until required for use.

Keep bottle tightly closed.

6.5 Nature and contents of container

RENVELA TABLETS are packaged in white, high-density polyethylene (HDPE) bottles, with a white, child-resistant polypropylene cap and a foil induction seal.

The bottle for the 30 tablets pack size is packaged in an outer carton.

Pack sizes: 30, 180, 270.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicine should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

sanofi-aventis south africa (pty) ltd

2 Bond Street

Midrand 1685

South Africa

8. REGISTRATION NUMBER

45/32.16/0305

9. DATE OF FIRST AUTHORISATION

05 June 2014

10. DATE OF REVISION OF THE TEXT

09 March 2022