Renvela® Abridged Prescribing Information:

1. NAME & PRESENTATION: Renvela 800 mg film-coated tablets, Each tablet contains 800 mg sevelamer carbonate.

2. Therapeutic INDICATIONS: Renvela is indicated for the control of hyperphosphatemia in adult patients receiving haemodialysis or

peritoneal dialysis.

Renvela is also indicated for the control of hyperphosphatemia in adult patients with chronic kidney disease not on dialysis with serum phosphorus > 1.78 mmol/l.

Renvela should be used within the context of a multiple therapeutic approach, which could include calcium supplement, 1,25-dihydroxy Vitamin D3 or one of its analogues to control the development of renal bone disease.

3. DOSAGE & POSOLOGY OF ADMINISTRATION: Starting dose

The recommended starting dose of sevelamer carbonate is 2.4 g or 4.8 g per day based on clinical needs and serum phosphorus level. Renvela must be taken three times per day with meals.

Serum phosphorus level in patients	Total daily dose of sevelamer carbonate to be taken over 3 meals per day
1.78 – 2.42 mmol/l (5.5 – 7.5 mg/dl)	2.4 g*
> 2.42 mmol/l (> 7.5 mg/dl)	4.8 g*

*Plus subsequent titrating as per instructions

For patients previously on phosphate binders (sevelamer hydrochloride or calcium based), Renvela 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 sevelamer carbonate titrated every 2-4 weeks until an acceptable serum phosphorus level is reached, with regular monitoring thereafter.

Patients taking Renvela 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.

Paediatric population

The safety and efficacy of Renvela has not been established in children below the age of 18 years.

Renvela is not recommended in children below the age of 18 years.

Method of administration

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

4. SPECIAL POPULATION: Paediatric population

The safety and efficacy of Renvela has not been established in children below the age of 18 years.

Renvela is not recommended in children below the age of 18 years.

4. CONTRA-INDICATIONS:

Hypersensitivity to the active substance or to any of the excipients., hypophosphatasemia, Bowel obstruction.

WARNINGS & PRECAUTIONS: Efficacy and safety of Renvela has not been studied in children below the age of 18 years.

The safety and efficacy of Renvela have not been established in adult patients with chronic kidney disease not on dialysis with serum phosphorus < 1.78 mmol/l. Therefore Renvela is currently not recommended for use in these patients.

The safety and efficacy of Renvela 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 Renvela is used in these patients.

6. INTERACTIONS: In interaction studies in healthy volunteers, sevelamer hydrochloride, which contains the same active moiety as Renvela, decreased the bioavailability of ciprofloxacin by approximately 50% when co-administered with sevelamer hydrochloride in a single dose study. Consequently, Renvela should not be taken simultaneously with ciprofloxacin.

Reduced levels of ciclosporin, mycophenolate mofetil and tacrolimus have been reported in transplant patients when co-administered with sevelamer hydrochloride without any clinical consequences (i.e graft rejection). The possibility of an interaction cannot be excluded and a close monitoring of blood concentrations of ciclosporin, mycophenolate mofetil and tacrolimus should be considered during the use of combination and after its withdrawal.

Very rare cases of hypothyroidism have been reported in patients co-administered sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, and levothyroxine. Closer monitoring of thyroid stimulating hormone (TSH) levels is therefore recommended in patients receiving sevelamer carbonate and levothyroxine.

7. PREGNANCY AND LACTATION: Pregnancy:

There are no data from the use of sevelamer in pregnant women. Studies in animals have shown some reproductive toxicity when sevelamer was administered to rats at high doses (see section 5.3). Sevelamer has also been shown to reduce the absorption of several vitamins including folic acid (see sections 4.4 and 5.3). The potential risk to humans is unknown. Renvela 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.

Lactation:

It is unknown whether sevelamer is excreted in human breast milk. The non-absorbed nature of sevelamer indicates that excretion of sevelamer in breast milk is unlikely. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Renvela should be made taking into account the benefit of breast-feeding to the child and the benefit of Renvela therapy to the woman.

8. EFFECTS ON ABILITY TO DRIVE: No studies on the effects on ability to drive and use machines have been performed.

9. ADVERSE REACTIONS: 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 treatment with sevelamer hydrochloride and 49 with sevelamer carbonate).

The most frequently occurring (≥ 5% of patients) undesirable effects possibly or probably related to sevelamer were all in the gastrointestinal disorders system organ class. Most of these adverse reactions were mild to moderate in intensity. Data possibly or probably related to sevelamer from these studies are listed by frequency in the table below. The reporting rate is classified as very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Gastrointestinal disorders

Very common : Nausea, vomiting, upper abdominal pain, constipation

Common : Diarrhoea, dyspepsia, flatulence, abdominal pain

Post-marketing experience: In very rare cases, intestinal obstruction and ileus/subileus have been observed in patients during treatment with sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate.

10.Overdose: No cases of overdose have been reported. Sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, has been given to normal healthy volunteers in doses of up to 14 grams per day for eight days with no undesirable effects. In CKD patients, the maximum average daily dose studied was 14.4 grams of sevelamer carbonate in a single daily dose.

11.Pharmacodynamics: Renvela contains sevelamer, a non-absorbed phosphate binding crosslinked polymer, free of metal and calcium. Sevelamer contains multiple amines separated by one carbon from the polymer backbone which become protonated in the stomach. These protonated amines bind negatively charged ions such as dietary phosphate in the intestine. By binding phosphate in the gastrointestinal tract and decreasing absorption, sevelamer lowers the phosphorus concentration in the serum. Regular monitoring of serum phosphorus levels is always necessary during phosphate binder administration.

In two randomised, cross over clinical studies, sevelamer carbonate in both tablet and powder formulations when administered three times per day has been shown to be therapeutically equivalent to sevelamer hydrochloride and therefore effective in controlling serum phosphorus in CKD patients on haemodialysis.

The first study demonstrated that sevelamer carbonate tablets dosed three times per day was equivalent to sevelamer hydrochloride tablets dosed three times per day in 79 haemodialysis patients treated over two randomised 8 week treatment periods (mean serum phosphorus time-weighted averages were 1.5 ± 0.3 mmol/l for both sevelamer carbonate and sevelamer hydrochloride). The second study demonstrated that sevelamer carbonate powder dosed three times per day was equivalent to sevelamer hydrochloride tablets dosed three times per day in 31 hyperphosphataemic (defined as serum phosphorus levels ≥ 1.78 mmol/l) haemodialysis patients over two randomised 4 week treatment periods (mean serum phosphorus time-weighted averages were 1.6 ± 0.5 mmol/l for sevelamer carbonate powder and 1.7 ± 0.4 mmol/l for sevelamer hydrochloride tablets).In the clinical studies in haemodialysis patients, sevelamer alone did not have a consistent and clinicallysignificant effect on serum intact parathyroid hormone (iPTH). In a 12 week study involving peritoneal dialysis patients however, similar iPTH reductions were seen compared with patients receiving calcium acetate. In patients with secondary hyperparathyroidism Renvela should be used within the context of a multiple therapeutic approach, which could include calcium as supplements, 1,25 – dihydroxy Vitamin D3 or one of its analogues to lower the intact parathyroid hormone (iPTH) levels.

Sevelamer has been shown to bind bile acids in vitro and in vivo in experimental animal models. Bile acid binding by ion exchange resins is a well-established method of lowering blood cholesterol. In clinical trials of sevelamer, both the mean total-cholesterol and LDL-cholesterol declined by 15-39%. The decrease in cholesterol has been observed after 2 weeks of treatment and is maintained with long-term treatment. Triglycerides, HDL-cholesterol and albumin levels did not change following sevelamer treatment.

Because sevelamer binds bile acids, it may interfere with the absorption of fat soluble vitamins such as A, D, E and K. Sevelamer does not contain calcium and decreases the incidence of hypercalcaemic episodes as compared to

patients using calcium based phosphate binders alone. The effects of sevelamer on phosphorus and calcium

were proven to be maintained throughout a study with one year

12. MARKETING AUTHORIZATION HOLDER: Genzyme Europe B.V. Gooimeer 10 1411 DD Naarden The Netherlands. Abbreviated Prescribing Information based on the EU SmPC as of January 2020. Always refer to the full Summary of Product Characteristics (SmPC) before prescribing