ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Renvela 800 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 800 mg sevelamer carbonate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).
The white to off-white tablets are imprinted with “RENVELA 800” on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Renvela is indicated for the control of hyperphosphataemia in adult patients receiving haemodialysis or peritoneal dialysis.

Renvela is also indicated for the control of hyperphosphataemia in adult patients with chronic kidney disease not on dialysis with serum phosphorus $\geq$ 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 D_3 or one of its analogues to control the development of renal bone disease.

4.2 Posology and method of administration

Posology

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 by 0.8 g three times per day (2.4 g/day) increments 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 have not been established in children below the age of 6 years or in children with a BSA below 0.75 m^2.

For paediatric patients the oral suspension should be administered, as tablet formulations are not appropriate for this population.

Method of administration
For oral use.
Tablets should be swallowed intact and should not be crushed, chewed, or broken into pieces prior to administration. Renvela should be taken with food and not on an empty stomach.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Hypophosphataemia
- Bowel obstruction.

4.4 Special warnings and precautions for use

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.

Intestinal obstruction and ileus/subileus
In very rare cases, intestinal obstruction and ileus/subileus have been observed in patients during treatment with sevelamer hydrochloride (capsules/tablets), which contains the same active moiety as sevelamer carbonate. Constipation may be a preceding symptom. Patients who are constipated should be monitored carefully while being treated with Renvela. Renvela treatment should be re-evaluated in patients who develop severe constipation or other severe gastrointestinal symptoms.

Fat-soluble vitamins
Patients with CKD may develop low levels of fat-soluble vitamins A, D, E and K, depending on dietary intake and the severity of their disease. It cannot be excluded that Renvela can bind fat-soluble vitamins contained in ingested food. In patients not taking supplemental vitamins but on sevelamer, serum vitamin A, D, E and 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. 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.

Folate deficiency
There is at present insufficient data to exclude the possibility of folate deficiency during long term Renvela treatment.

Hypocalcaemia/hypercalcaemia
Patients with CKD may develop hypocalcaemia or hypercalcaemia. Renvela does not contain any calcium. Serum calcium levels should therefore be monitored at regular intervals and elemental calcium should be given as a supplement if required.

Metabolic acidosis
Patients with chronic kidney disease are predisposed to developing metabolic acidosis. As part of good clinical practice, monitoring of serum bicarbonate levels is therefore recommended.

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 study 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.

Swallowing and choking difficulties
Uncommon reports of difficulty swallowing the Renvela tablet have been reported. Many of these cases involved patients with co-morbid conditions including swallowing disorders or oesophageal abnormalities. Caution should be exercised when Renvela is used in patients with difficulty swallowing. The use of Renvela powder for oral suspension in patients with a history of difficulty swallowing should be considered.

Hypothyroidism
Closer monitoring of patients with hypothyroidism co-administered with sevelamer carbonate and levothyroxine is recommended (see section 4.5).

Long-term chronic treatment
In a clinical trial of one year, no evidence of accumulation of sevelamer was seen. However the potential absorption and accumulation of sevelamer during long-term chronic treatment (> one year) cannot be totally excluded (see section 5.2).

Hyperparathyroidism
Renvela is not indicated for the control of hyperparathyroidism. 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 D_3 or one of its analogues to lower the intact parathyroid hormone (iPTH) levels.

Inflammatory Gastrointestinal Disorders
Cases of serious inflammatory disorders of different parts of the gastrointestinal tract (including serious complications such as bleeding, perforation, ulceration, necrosis, colitis, …) associated with the presence of sevelamer crystals have been reported in literature. However, the causality of the sevelamer crystals in initiating such disorders has not been demonstrated. Sevelamer carbonate treatment should be re-evaluated in patients who develop severe gastrointestinal symptoms.

4.5 Interaction with other medicinal products and other forms of interaction

Dialysis
Interaction studies have not been conducted in patients on dialysis.

Ciprofloxacin
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.

Ciclosporin, mycophenolate mofetil and tacrolimus in transplant patients
Reduced levels of ciclosporin, mycophenolate mofetil and tacrolimus have been reported in transplant patients when co-administered with sevelamer hydrochloride without any clinical consequences (e.g., 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.

Levothyroxine
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.

Anti-arrhythmics and anti-seizure medicinal products
Patients taking anti-arrhythmic medicinal products for the control of arrhythmias and anti-seizure medicinal products for the control of seizure disorders were excluded from clinical trials. Caution should be exercised when prescribing Renvela to patients also taking these medicinal products.

Digoxin, warfarin, enalapril or metoprolol
In interaction studies in healthy volunteers, sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, had no effect on the bioavailability of digoxin, warfarin, enalapril or metoprolol.

Proton pump inhibitors
During post-marketing experience, very rare cases of increased phosphate levels have been reported in patients taking proton pump inhibitors co-administered with sevelamer carbonate.

Bioavailability
Renvela is not absorbed and may affect the bioavailability of other medicinal products. When administering any medicinal product where a reduction in the bioavailability could have a clinically significant effect on safety or efficacy, the medicinal product should be administered at least one hour before or three hours after Renvela, or the physician should consider monitoring blood levels.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of sevelamer in pregnant women. Animal studies 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.

Breast-feeding
It is unknown whether sevelamer/metabolites are excreted in human 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.

Fertility

There are no data from the effect of sevelamer on fertility in humans. Studies in animals have shown that sevelamer did not impair fertility in male or female rats at exposures at a human equivalent dose 2 times the maximum clinical trial dose of 13 g/day, based on a comparison of relative body surface area.

4.7 Effects on ability to drive and use machines

Sevelamer has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The most frequently occurring (≥ 5% of patients) adverse reactions were all in the gastrointestinal disorders system organ class. Most of these adverse reactions were mild to moderate in intensity.

Tabulated list of 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).

Adverse reactions that occurred during clinical studies or that were spontaneously reported from post-marketing experience are listed by frequency in the table below. The reporting rate is classified as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

MedDRA System Organ Class	Very Common	Common	Very Rare	Not known
Immune system disorders			Hypersensitivity*	
Gastrointestinal disorders	Nausea, vomiting, upper abdominal pain, constipation	Diarrhoea, dyspepsia, flatulence, abdominal pain		Intestinal obstruction, ileus/subileus, intestinal perforation
Skin and subcutaneous tissue disorders				Pruritus, rash

**post-marketing experience*

Paediatric population
In general, the safety profile for children and adolescents (6 to 18 years of age) is similar to the safety profile for adults.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Treatment of hyperphosphataemia. ATC code: V03A E02.

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 clinically significant 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 D_3 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 follow-up. This information was obtained from studies in which sevelamer hydrochloride was used.

The safety and effectiveness of sevelamer carbonate in hyperphosphatemic paediatric patients with Chronic Kidney Disease (CKD) was evaluated in a multicenter study with a 2-week, randomized, placebo-controlled, Fixed Dose Period (FDP) followed by a 6-month, single-arm, open-label, Dose Titration Period (DTP). A total of 101 patients (6 to 18 years old with a BSA range of 0.8 m^2 to 2.4 m^2) were randomized in the study. Forty-nine (49) patients received sevelamer carbonate and 51 received placebo during the 2 week FDP. Thereafter all patients received sevelamer carbonate for the 26-week DTP. The study met its primary

endpoint, meaning Sevelamer carbonate reduced serum phosphorus by an LS mean difference of -0.90 mg/dL compared to placebo, and secondary efficacy endpoints. In paediatric patients with hyperphosphatemia secondary to CKD, sevelamer carbonate significantly reduced serum phosphorus levels compared to placebo during a 2-week FDP. The treatment response was maintained in the paediatric patients who received sevelamer carbonate during the 6-month open-label DTP. 27% of paediatric patients reached their age appropriate serum phosphorus level at end of treatment. These figures were 23% and 15% in the subgroup of patients on hemodialysis and peritoneal dialysis, respectively. The treatment response during the 2-week FDP was not affected by body surface area (BSA), in contrast however, no treatment response was observed in pediatric patients with qualifying phosphorus levels <7.0 mg/dL. Most of AEs reported as related, or possibly related, to sevelamer carbonate were gastrointestinal in nature. No new risks or safety signals were identified with the use of sevelamer carbonate during the study.

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

Non-clinical data with sevelamer reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity or genotoxicity.

Carcinogenicity studies with oral sevelamer hydrochloride were conducted in mice (doses of up to 9 g/kg/day) and rats (0.3, 1, or 3 g/kg/day). There was an increased incidence of urinary bladder transitional cell papilloma in male rats of the high dose group (human equivalent dose twice the maximum clinical trial dose of 14.4 g). There was no increased incidence of tumors observed in mice (human equivalent dose 3 times the maximum clinical trial dose).

In an *in vitro* mammalian cytogenetic test with metabolic activation, sevelamer hydrochloride caused a statistically significant increase in the number of structural chromosome aberrations. Sevelamer hydrochloride was not mutagenic in the Ames bacterial mutation assay.

In rats and dogs, sevelamer reduced absorption of fat soluble vitamins D, E and K (coagulation factors), and folic acid.

Deficits in skeletal ossification were observed in several locations in foetuses of female rats dosed with sevelamer at intermediate and high doses (human equivalent dose less than the maximum clinical trial dose of 14.4 g). The effects may be secondary to vitamin D depletion.

In pregnant rabbits given oral doses of sevelamer hydrochloride by gavage during organogenesis, an increase of early resorptions occurred in the high-dose group (human equivalent dose twice the maximum clinical trial dose).

Sevelamer hydrochloride did not impair the fertility of male or female rats in a dietary administration study in which the females were treated from 14 days prior to mating through gestation and the males were treated for 28 days prior to mating. The highest dose in this study was 4.5 g/kg/day (human equivalent dose 2 times the maximum clinical trial dose of 13 g/day, based on a comparison of relative body surface area).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Microcrystalline cellulose

Sodium chloride
Zinc stearate

Film-coating:
Hypromellose (E464)
Diacetylated monoglycerides

Printing ink:
Iron oxide black (E172)
Propylene glycol
Isopropyl alcohol
Hypromellose (E464)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Keep the bottle tightly closed in order to protect from moisture.

This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

HDPE bottles with a polypropylene cap and a foil induction seal.
Each bottle contains 30 tablets or 180 tablets.
Packs of 30 or 180 tablets and a multipack containing 180 (6 bottles of 30) tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Genzyme Europe B.V.
Gooimeer 10
1411 DD Naarden
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/521/001
EU/1/09/521/002
EU/1/09/521/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10 June 2009
Date of latest renewal: 21 March 2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/

1.NAME OF THE MEDICINAL PRODUCT

Renvela 1.6 g powder for oral suspension

2.QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains 1.6 g sevelamer carbonate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for oral suspension.
Pale yellow powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Renvela is indicated for the control of hyperphosphataemia in adult patients receiving haemodialysis or peritoneal dialysis.

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

Renvela is indicated for the control of hyperphosphataemia in paediatric patients (>6 years of age and a Body Surface Area (BSA) of >0.75 m^2) with chronic kidney disease.

Renvela should be used within the context of a multiple therapeutic approach, which could include calcium supplement, 1,25-dihydroxy Vitamin D_3 or one of its analogues to control the development of renal bone disease.

4.2 Posology and method of administration

Posology:

Starting dose
Adults
The recommended starting dose of sevelamer carbonate for adults is 2.4 g or 4.8 g per day based on clinical needs and serum phosphorus level. Renvela powder for oral suspension 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

Children/adolescents (>6 years of age and a body surface area (BSA) of >0.75m^2)
The recommended starting dose of sevelamer carbonate for children is between 2.4 g and 4.8 g per day based on the patient's body surface area (BSA) category. Renvela must be taken three times per day with meals or snacks.

BSA (m^2)	Total daily dose of sevelamer carbonate to be taken over 3 meals/snacks per day
>0.75 to <1.2	2.4 g**
≥1.2	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

*Adults

For adult patients, serum phosphorus levels must be monitored and the dose of sevelamer carbonate titrated by 0.8 g three times per day (2.4 g/day) increments every 2-4 weeks until an acceptable serum phosphorus level is reached, with regular monitoring thereafter.

In clinical practice, treatment will be continuous based on the need to control serum phosphorus levels and the daily adult dose is expected to be an average of approximately 6 g per day.

**Children and adolescents (>6 years of age and a body surface area (BSA) of >0.75m^2)

For paediatric patients, serum phosphorus levels must be monitored and the dose of sevelamer carbonate titrated in increments based on patient's BSA, three times per day every 2-4 weeks until an acceptable serum phosphorus level is reached, with regular monitoring thereafter.

Paediatric dosage based on body surface area (BSA) (m^2)

BSA (m^2)	Starting dose	Titration increases/decreases
>0.75 to <1.2	0.8 g three times daily	Titrate up/down by 0.4 g three times daily
≥1.2	1.6 g three times daily	Titrate up/down by 0.8 g three times daily

Patients taking Renvela should adhere to their prescribed diets.

Paediatric population

The safety and efficacy of Renvela have not been established in children below the age of 6 years or in children with a BSA below 0.75 m^2.

For paediatric patients with a <1.2 BSA (m^2), the oral suspension should be administered, as tablet formulations were not tested in this population and therefore are not appropriate for this population.

Method of administration:

For oral use.

Each sachet of 1.6 g of powder is to be dispersed in 40 *mL* of water prior to administration (see section 6.6). The suspension should be ingested within 30 minutes after being prepared. Renvela should be taken with food and not on an empty stomach.

To achieve the correct dose, a 1.6 g sachet of Renvela powder may be divided. The Renvela powder may be measured by volume (mL) using a measuring scoop or measuring spoon. Further instructions are detailed in the Patient Leaflet.

Sevelamer carbonate dose (g)	**Volume (mL)**
0.4 g (400 mg)	1.0 mL
0.8 g (800 mg)	2.0 mL
1.2 g (1200 mg)	3.0 mL
1.6 g (1600 mg)	4.0 mL

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Hypophosphataemia
- Bowel obstruction.

4.4 Special warnings and precautions for use

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.

Intestinal obstruction and ileus/subileus

In very rare cases, intestinal obstruction and ileus/subileus have been observed in patients during treatment with sevelamer hydrochloride (capsules/tablets), which contains the same active moiety as sevelamer carbonate. Constipation may be a preceding symptom. Patients who are constipated should be monitored carefully while being treated with Renvela. Renvela treatment should be re-evaluated in patients who develop severe constipation or other severe gastrointestinal symptoms.

Fat-soluble vitamins

Patients with CKD may develop low levels of fat-soluble vitamins A, D, E and K, depending on dietary intake and the severity of their disease. It cannot be excluded that Renvela can bind fat-soluble vitamins contained in ingested food. In patients not taking supplemental vitamins but on sevelamer, serum vitamin A, D, E and 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. 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.

Folate deficiency

There is at present insufficient data to exclude the possibility of folate deficiency during long term Renvela treatment.

Hypocalcaemia/hypercalcaemia

Patients with CKD may develop hypocalcaemia or hypercalcaemia. Renvela does not contain any calcium. Serum calcium levels should therefore be monitored at regular intervals and elemental calcium should be given as a supplement if required.

Metabolic acidosis

Patients with chronic kidney disease are predisposed to developing metabolic acidosis. As part of good clinical practice, monitoring of serum bicarbonate levels is therefore recommended.

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 study 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.

Swallowing and choking difficulties
Uncommon reports of difficulty swallowing the Renvela tablet have been reported. Many of these cases involved patients with co-morbid conditions including swallowing disorders or oroesophageal abnormalities. Caution should be exercised when Renvela is used in patients with difficulty swallowing. The use of Renvela powder for oral suspension in patients with a history of difficulty swallowing should be considered.

Hypothyroidism
Closer monitoring of patients with hypothyroidism co-administered with sevelamer carbonate and levothyroxine is recommended (see section 4.5).

Long-term chronic treatment
In a clinical trial of one year, no evidence of accumulation of sevelamer was seen. However the potential absorption and accumulation of sevelamer during long-term chronic treatment (> one year) cannot be totally excluded (see section 5.2).

Hyperparathyroidism
Renvela is not indicated for the control of hyperparathyroidism. 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 D_3 or one of its analogues to lower the intact parathyroid hormone (iPTH) levels.

Inflammatory Gastrointestinal Disorders
Cases of serious inflammatory disorders of different parts of the gastrointestinal tract (including serious complications such as bleeding, perforation, ulceration, necrosis, colitis, …) associated with the presence of sevelamer crystals have been reported in literature. However, the causality of the sevelamer crystals in initiating such disorders has not been demonstrated. Sevelamer carbonate treatment should be re-evaluated in patients who develop severe gastrointestinal symptoms.

4.5 Interaction with other medicinal products and other forms of interaction

Dialysis
Interaction studies have not been conducted in patients on dialysis.

Ciprofloxacin
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.

Ciclosporin, mycophenolate mofetil and tacrolimus in transplant patients
Reduced levels of ciclosporin, mycophenolate mofetil and tacrolimus have been reported in transplant patients when co-administered with sevelamer hydrochloride without any clinical consequences (e.g., 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.

Levothyroxine
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.

Anti-arrhythmics and anti-seizure medicinal products
Patients taking anti-arrhythmic medicinal products for the control of arrhythmias and anti-seizure medicinal products for the control of seizure disorders were excluded from clinical trials. Caution should be exercised when prescribing Renvela to patients also taking these medicinal products.

Digoxin, warfarin, enalapril or metoprolol
In interaction studies in healthy volunteers, sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, had no effect on the bioavailability of digoxin, warfarin, enalapril or metoprolol.

Proton pump inhibitors
During post-marketing experience, very rare cases of increased phosphate levels have been reported in patients taking proton pump inhibitors co-administered with sevelamer carbonate.

Bioavailability
Renvela is not absorbed and may affect the bioavailability of other medicinal products. When administering any medicinal product where a reduction in the bioavailability could have a clinically significant effect on safety or efficacy, the medicinal product should be administered at least one hour before or three hours after Renvela, or the physician should consider monitoring blood levels.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of sevelamer in pregnant women. Animal studies 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.

Breast-feeding
It is unknown whether sevelamer/metabolites are excreted in human 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.

Fertility
There are no data from the effect of sevelamer on fertility in humans. Studies in animals have shown that sevelamer did not impair fertility in male or female rats at exposures at a human equivalent dose 2 times the maximum clinical trial dose of 13 g/day, based on a comparison of relative body surface area.

4.7 Effects on ability to drive and use machines

Sevelamer has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The most frequently occurring (≥ 5% of patients) adverse reactions were all in the gastrointestinal disorders system organ class. Most of these adverse reactions were mild to moderate in intensity.

Tabulated list of 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).

Adverse reactions that occurred during clinical studies or that were spontaneously reported from post-marketing experience are listed by frequency in the table below. The reporting rate is classified as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from available data).

MedDRA System Organ Class	Very Common	Common	Very Rare	Not known
Immune system disorders			Hypersensitivity*	
Gastrointestinal disorders	Nausea, vomiting, upper abdominal pain, constipation	Diarrhoea, dyspepsia, flatulence, abdominal pain		Intestinal obstruction, ileus/subileus, intestinal perforation
Skin and subcutaneous tissue disorders				Pruritus, rash

**post-marketing experience*

Paediatric population
In general, the safety profile for children and adolescents (6 to 18 years of age) is similar to the safety profile for adults.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Treatment of hyperphosphataemia. ATC code: V03A E02.

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 has been shown to be therapeutically equivalent to sevelamer hydrochloride and therefore effective in controlling serum phosphorus in CKD patients on haemodialysis. These also demonstrated that sevelamer carbonate in both tablet and powder formulations are therapeutically equivalent to sevelamer hydrochloride.

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 clinically significant effect on serum intact parathyroid hormone (iPTH). In the 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 D_3 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 follow-up. This information was obtained from studies in which sevelamer hydrochloride was used.

The safety and effectiveness of sevelamer carbonate in hyperphosphatemic paediatric patients with Chronic Kidney Disease (CKD) was evaluated in a multicenter study with a 2-week, randomized, placebo-controlled, Fixed Dose Period (FDP) followed by a 6-month, single-arm, open-label, Dose Titration Period (DTP). A total of 101 patients (6 to 18 years old with a BSA range of 0.8 m^2 to 2.4 m^2) were randomized in the study. Forty-nine (49) patients received sevelamer carbonate and 51 received placebo during the 2 week FDP. Thereafter all patients received sevelamer carbonate for the 26-week DTP. The study met its primary endpoint, meaning Sevelamer carbonate reduced serum phosphorus by an LS mean difference of -0.90 mg/dL compared to placebo, and secondary efficacy endpoints. In paediatric patients with hyperphosphatemia secondary to CKD, sevelamer carbonate significantly reduced serum phosphorus levels compared to placebo during a 2-week FDP. The treatment response was maintained in the paediatric patients who received sevelamer carbonate during the 6-month open-label DTP. 27% of paediatric patients reached their age appropriate serum phosphorus level at end of treatment. These figures were 23% and 15% in the subgroup of patients on hemodialysis and peritoneal dialysis, respectively. The treatment response during the 2-week FDP was not affected by body surface area (BSA), in contrast however, no treatment response was observed in pediatric patients with qualifying phosphorus levels <7.0 mg/dL. Most of AEs reported as related, or possibly related, to sevelamer carbonate were gastrointestinal in nature. No new risks or safety signals were identified with the use of sevelamer carbonate during the study.

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

Non-clinical data with sevelamer reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity or genotoxicity.

Carcinogenicity studies with oral sevelamer hydrochloride were conducted in mice (doses of up to 9 g/kg/day) and rats (0.3, 1, or 3 g/kg/day). There was an increased incidence of urinary bladder transitional cell papilloma in male rats of the high dose group (human equivalent dose twice the maximum clinical trial dose of 14.4 g). There was no increased incidence of tumors observed in mice (human equivalent dose 3 times the maximum clinical trial dose).

In an *in vitro* mammalian cytogenetic test with metabolic activation, sevelamer hydrochloride caused a statistically significant increase in the number of structural chromosome aberrations. Sevelamer hydrochloride was not mutagenic in the Ames bacterial mutation assay.

In rats and dogs, sevelamer reduced absorption of fat soluble vitamins D, E and K (coagulation factors), and folic acid.

Deficits in skeletal ossification were observed in several locations in foetuses of female rats dosed with sevelamer at intermediate and high doses (human equivalent dose less than the maximum clinical trial dose of 14.4 g). The effects may be secondary to vitamin D depletion.

In pregnant rabbits given oral doses of sevelamer hydrochloride by gavage during organogenesis, an increase of early resorptions occurred in the high-dose group (human equivalent dose twice the maximum clinical trial dose).

Sevelamer hydrochloride did not impair the fertility of male or female rats in a dietary administration study in which the females were treated from 14 days prior to mating through gestation and the males were treated for 28 days prior to mating. The highest dose in this study was 4.5 g/kg/day (human equivalent dose 2 times the maximum clinical trial dose of 13 g/day, based on a comparison of relative body surface area).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Propylene glycol alginate
Citrus Cream flavour
Sodium chloride
Sucralose
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

The reconstituted suspension must be administered within 30 minutes of reconstitution.

6.4 Special precautions for storage

The medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Sachet of ethylene methacrylic acid copolymer, polyester, low density polyethylene and aluminium foil laminate, with a heat seal.
Each sachet contains 1.6g of sevelamer carbonate. Each carton contains 60 or 90 sachets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The powder should be dispersed in 40 mL of water per sachet prior to administration. The suspension powder is pale yellow and has a citrus flavour.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Genzyme Europe B.V.
Gooimeer 10
1411 DD Naarden
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/521/004
EU/1/09/521/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10 June 2009
Date of latest renewal: 21 March 2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

1. NAME OF THE MEDICINAL PRODUCT

Renvela 2.4 g powder for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains 2.4 g sevelamer carbonate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for oral suspension.
Pale yellow powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Renvela is indicated for the control of hyperphosphataemia in adult patients receiving haemodialysis or peritoneal dialysis.

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

Renvela is indicated for the control of hyperphosphataemia in paediatric patients (>6 years of age and a Body Surface Area (BSA) of >0.75 m^2) with chronic kidney disease.

Renvela should be used within the context of a multiple therapeutic approach, which could include calcium supplement, 1,25-dihydroxy Vitamin D_3 or one of its analogues to control the development of renal bone disease.

4.2 Posology and method of administration

Posology:

Starting dose
Adults
The recommended starting dose of sevelamer carbonate for adults is 2.4 g or 4.8 g per day based on clinical needs and serum phosphorus level. Renvela powder for oral suspension 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

Children/adolescents (>6 years of age and a body surface area (BSA) of >0.75m^2)
The recommended starting dose of sevelamer carbonate for children is between 2.4 g and 4.8 g per day based on the patient's body surface area (BSA) category. Renvela must be taken three times per day with meals or snacks.

BSA (m^2)	Total daily dose of sevelamer carbonate to be taken over 3 meals/snacks per day
>0.75 to <1.2	2.4 g**
≥1.2	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

*Adults

For adult patients, serum phosphorus must be monitored and the dose of sevelamer carbonate titrated by 0.8 g three times per day (2.4 g/day) increments every 2-4 weeks until an acceptable serum phosphorus level is reached, with regular monitoring thereafter.

In clinical practice, treatment will be continuous based on the need to control serum phosphorus levels and the daily adult dose is expected to be an average of approximately 6 g per day.

**Children and adolescents (>6 years of age and a body surface area (BSA) of >0.75m^2)

For paediatric patients, serum phosphorus levels must be monitored and the dose of sevelamer carbonate titrated in increments based on patient's BSA, three times per day every 2-4 weeks until an acceptable serum phosphorus level is reached, with regular monitoring thereafter.

Paediatric dosage based on body surface area (BSA) (m^2)

BSA (m^2)	Starting dose	Titration increases/decreases
>0.75 to <1.2	0.8 g three times daily	Titrate up/down by 0.4 g three times daily
≥1.2	1.6 g three times daily	Titrate up/down by 0.8 g three times daily

Patients taking Renvela should adhere to their prescribed diets.

Paediatric population

The safety and efficacy of Renvela have not been established in children below the age of 6 years or in children with a BSA below 0.75 m^2.

For paediatric patients with a <1.2 BSA (m^2), the oral suspension should be administered, as tablet formulations were not tested in this population and therefore are not appropriate for this population.

Method of administration

For oral use.

Each sachet of 2.4 g of powder is to be dispersed in 60 mL of water prior to administration (see section 6.6). The suspension should be ingested within 30 minutes after being prepared. Renvela should be taken with food and not on an empty stomach.

To achieve the correct dose, a 2.4 g sachet of Renvela powder may be divided. The Renvela powder may be measured by volume (mL) using a measuring scoop or measuring spoon. Further instructions are detailed in the Patient Leaflet.

Sevelamer carbonate dose (g)	**Volume (mL)**
0.4 g (400 mg)	1.0 mL
0.8 g (800 mg)	2.0 mL
1.2 g (1200 mg)	3.0 mL
1.6 g (1600 mg)	4.0 mL

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Hypophosphataemia
- Bowel obstruction.

4.4 Special warnings and precautions for use

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.

Intestinal obstruction and ileus/subileus
In very rare cases, intestinal obstruction and ileus/subileus have been observed in patients during treatment with sevelamer hydrochloride (capsules/tablets), which contains the same active moiety as sevelamer carbonate. Constipation may be a preceding symptom. Patients who are constipated should be monitored carefully while being treated with Renvela. Renvela treatment should be re-evaluated in patients who develop severe constipation or other severe gastrointestinal symptoms.

Fat-soluble vitamins
Patients with CKD may develop low levels of fat-soluble vitamins A, D, E and K, depending on dietary intake and the severity of their disease. It cannot be excluded that Renvela can bind fat-soluble vitamins contained in ingested food. In patients not taking supplemental vitamins but on sevelamer, serum vitamin A, D, E and 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. 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.

Folate deficiency
There is at present insufficient data to exclude the possibility of folate deficiency during long term Renvela treatment.

Hypocalcaemia/hypercalcaemia
Patients with CKD may develop hypocalcaemia or hypercalcaemia. Renvela does not contain any calcium. Serum calcium levels should therefore be monitored at regular intervals and elemental calcium should be given as a supplement if required.

Metabolic acidosis
Patients with chronic kidney disease are predisposed to developing metabolic acidosis. As part of good clinical practice, monitoring of serum bicarbonate levels is therefore recommended.

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 study 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.

Swallowing and choking difficulties
Uncommon reports of difficulty swallowing the Renvela tablet have been reported. Many of these cases involved patients with co-morbid conditions including swallowing disorders or oroesophageal abnormalities. Caution should be exercised when Renvela is used in patients with difficulty swallowing. The use of Renvela powder for oral suspension in patients with a history of difficulty swallowing should be considered.

Hypothyroidism
Closer monitoring of patients with hypothyroidism co-administered with sevelamer carbonate and levothyroxine is recommended (see section 4.5).

Long-term chronic treatment
In a clinical trial of one year, no evidence of accumulation of sevelamer was seen. However the potential absorption and accumulation of sevelamer during long-term chronic treatment (> one year) cannot be totally excluded (see section 5.2).

Hyperparathyroidism
Renvela is not indicated for the control of hyperparathyroidism. 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 D_3 or one of its analogues to lower the intact parathyroid hormone (iPTH) levels.

Inflammatory Gastrointestinal Disorders
Cases of serious inflammatory disorders of different parts of the gastrointestinal tract (including serious complications such as bleeding, perforation, ulceration, necrosis, colitis, …) associated with the presence of sevelamer crystals have been reported in literature. However, the causality of the sevelamer crystals in initiating such disorders has not been demonstrated. Sevelamer carbonate treatment should be re-evaluated in patients who develop severe gastrointestinal symptoms.

4.5 Interaction with other medicinal products and other forms of interaction

Dialysis
Interaction studies have not been conducted in patients on dialysis.

Ciprofloxacin
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.

Ciclosporin, mycophenolate mofetil and tacrolimus in transplant patients
Reduced levels of ciclosporin, mycophenolate mofetil and tacrolimus have been reported in transplant patients when co-administered with sevelamer hydrochloride without any clinical consequences (e.g., 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.

Levothyroxine
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.

Anti-arrhythmics and anti-seizure medicinal products
Patients taking anti-arrhythmic medicinal products for the control of arrhythmias and anti-seizure medicinal products for the control of seizure disorders were excluded from clinical trials. Caution should be exercised when prescribing Renvela to patients also taking these medicinal products.

Digoxin, warfarin, enalapril or metoprolol
In interaction studies in healthy volunteers, sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, had no effect on the bioavailability of digoxin, warfarin, enalapril or metoprolol.

Proton pump inhibitors
During post-marketing experience, very rare cases of increased phosphate levels have been reported in patients taking proton pump inhibitors co-administered with sevelamer carbonate.

Bioavailability
Renvela is not absorbed and may affect the bioavailability of other medicinal products. When administering any medicinal product where a reduction in the bioavailability could have a clinically significant effect on safety or efficacy, the medicinal product should be administered at least one hour before or three hours after Renvela, or the physician should consider monitoring blood levels.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of sevelamer in pregnant women. Animal studies 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.

Breast-feeding
It is unknown whether sevelamer/metabolites are excreted in human 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.

Fertility
There are no data from the effect of sevelamer on fertility in humans. Studies in animals have shown that sevelamer did not impair fertility in male or female rats at exposures at a human equivalent dose 2 times the maximum clinical trial dose of 13 g/day, based on a comparison of relative body surface area.

4.7 Effects on ability to drive and use machines

Sevelamer has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The most frequently occurring (≥ 5% of patients) adverse reactions were all in the gastrointestinal disorders system organ class. Most of these adverse reactions were mild to moderate in intensity.

Tabulated list of 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).

Adverse reactions that occurred during clinical studies or that were spontaneously reported from post-marketing experience are listed by frequency in the table below. The reporting rate is classified as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

MedDRA System Organ Class	Very Common	Common	Very Rare	Not known
Immune system disorders			Hypersensitivity*	
Gastrointestinal disorders	Nausea, vomiting, upper abdominal pain, constipation	Diarrhoea, dyspepsia, flatulence, abdominal pain		Intestinal obstruction, ileus/subileus, intestinal perforation
Skin and subcutaneous tissue disorders				Pruritus, rash

**post-marketing experience*

Paediatric population
In general, the safety profile for children and adolescents (6 to 18 years of age) is similar to the safety profile for adults.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Treatment of hyperphosphataemia. ATC code: V03A E02.

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 has been shown to be therapeutically equivalent to sevelamer hydrochloride and therefore effective in controlling serum phosphorus in CKD patients on haemodialysis. These also demonstrated that sevelamer carbonate in both tablet and powder formulations are therapeutically equivalent to sevelamer hydrochloride.

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 clinically significant 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 D_3 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 follow-up. This information was obtained from studies in which sevelamer hydrochloride was used.

The safety and effectiveness of sevelamer carbonate in hyperphosphatemic paediatric patients with Chronic Kidney Disease (CKD) was evaluated in a multicenter study with a 2-week, randomized, placebo-controlled, Fixed Dose Period (FDP) followed by a 6-month, single-arm, open-label, Dose Titration Period (DTP). A total of 101 patients (6 to 18 years old with a BSA range of 0.8 m^2 to 2.4 m^2) were randomized in the study. Forty-nine (49) patients received sevelamer carbonate and 51 received placebo during the 2 week FDP. Thereafter all patients received sevelamer carbonate for the 26-week DTP. The study met its primary endpoint, meaning Sevelamer carbonate reduced serum phosphorus by an LS mean difference of -0.90 mg/dL compared to placebo, and secondary efficacy endpoints. In paediatric patients with hyperphosphatemia secondary to CKD, sevelamer carbonate significantly reduced serum phosphorus levels compared to placebo during a 2-week FDP. The treatment response was maintained in the paediatric patients who received sevelamer carbonate during the 6-month open-label DTP. 27% of paediatric patients reached their age appropriate serum phosphorus level at end of treatment. These figures were 23% and 15% in the subgroup of patients on hemodialysis and peritoneal dialysis, respectively. The treatment response during the 2-week FDP was not affected by body surface area (BSA), in contrast however, no treatment response was observed in pediatric patients with qualifying phosphorus levels <7.0 mg/dL. Most of AEs reported as related, or possibly related, to sevelamer carbonate were gastrointestinal in nature. No new risks or safety signals were identified with the use of sevelamer carbonate during the study.

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

Non-clinical data with sevelamer reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity or genotoxicity.

Carcinogenicity studies with oral sevelamer hydrochloride were conducted in mice (doses of up to 9 g/kg/day) and rats (0.3, 1, or 3 g/kg/day). There was an increased incidence of urinary bladder transitional cell papilloma in male rats of the high dose group (human equivalent dose twice the maximum clinical trial dose of 14.4 g). There was no increased incidence of tumors observed in mice (human equivalent dose 3 times the maximum clinical trial dose).

In an *in vitro* mammalian cytogenetic test with metabolic activation, sevelamer hydrochloride caused a statistically significant increase in the number of structural chromosome aberrations. Sevelamer hydrochloride was not mutagenic in the Ames bacterial mutation assay.

In rats and dogs, sevelamer reduced absorption of fat soluble vitamins D, E and K (coagulation factors), and folic acid.

Deficits in skeletal ossification were observed in several locations in foetuses of female rats dosed with sevelamer at intermediate and high doses (human equivalent dose less than the maximum clinical trial dose of 14.4 g). The effects may be secondary to vitamin D depletion.

In pregnant rabbits given oral doses of sevelamer hydrochloride by gavage during organogenesis, an increase of early resorptions occurred in the high-dose group (human equivalent dose twice the maximum clinical trial dose).

Sevelamer hydrochloride did not impair the fertility of male or female rats in a dietary administration study in which the females were treated from 14 days prior to mating through gestation and the males were treated for 28 days prior to mating. The highest dose in this study was 4.5 g/kg/day (human equivalent dose 2 times the maximum clinical trial dose of 13 g/day, based on a comparison of relative body surface area).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Propylene glycol alginate
Citrus Cream flavour
Sodium chloride
Sucralose
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

The reconstituted suspension must be administered within 30 minutes of reconstitution.

6.4 Special precautions for storage

The medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Sachet of ethylene methacrylic acid copolymer, polyester, low density polyethylene and aluminium foil laminate, with a heat seal.
Each sachet contains 2.4g of sevelamer carbonate. Each carton contains 60 or 90 sachets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The powder should be dispersed in 60 mL of water per sachet prior to administration. The suspension powder is pale yellow with a citrus flavour.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Genzyme Europe B.V.
Gooimeer 10
1411 DD Naarden
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/521/006
EU/1/09/521/007

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10 June 2009
Date of latest renewal: 21 March 2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Genzyme Ltd.
37 Hollands Road
Haverhill, Suffolk
CB9 8PB
United Kingdom

Genzyme Ireland Ltd.
IDA Industrial Park
Old Kilmeaden Road
Waterford
Ireland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the medicinal product is on the market.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

LABEL - BOTTLE OF 30 TABLETS (WITH OUTER CARTON)
LABEL with Blue box - BOTTLE OF 180 TABLETS (WITHOUT OUTER CARTON)

1. NAME OF THE MEDICINAL PRODUCT

Renvela 800 mg film-coated tablets
sevelamer carbonate

2. STATEMENT OF ACTIVE SUBSTANCE

Each tablet contains 800 mg sevelamer carbonate.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets
180 film-coated tablets

5. METHOD AND ROUTE OF ADMINISTRATION

For oral use.
Tablets must be swallowed whole. Do not chew.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep the bottle tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Genzyme Europe B.V.
Gooimeer 10
1411 DD Naarden
The Netherlands

12. MARKETING AUTHORISATION NUMBERS

EU/1/09/521/001 30 film-coated tablets
EU/1/09/521/003 180 film-coated tablets

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Renvela
800 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON with Blue box – BOTTLE OF 30 TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Renvela 800 mg film-coated tablets
sevelamer carbonate

2. STATEMENT OF ACTIVE SUBSTANCE

Each tablet contains 800 mg sevelamer carbonate.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets

5. METHOD AND ROUTE OF ADMINISTRATION

For oral use.
Tablets must be swallowed whole. Do not chew.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep bottle tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Genzyme Europe B.V.
Gooimeer 10
1411 DD Naarden
The Netherlands

12. MARKETING AUTHORISATION NUMBERS

EU/1/09/521/001

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Renvela
800 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

LABEL - BOTTLE OF 30 TABLETS (MULTIPACK PRESENTATION)

1. NAME OF THE MEDICINAL PRODUCT

Renvela 800 mg film-coated tablets
sevelamer carbonate

2. STATEMENT OF ACTIVE SUBSTANCE

Each tablet contains 800 mg sevelamer carbonate.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE OF ADMINISTRATION

For oral use.
Tablets must be swallowed whole. Do not chew.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep the bottle tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Genzyme Europe B.V.
Gooimeer 10
1411 DD Naarden
The Netherlands

12. MARKETING AUTHORISATION NUMBERS

EU/1/09/521/002

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Renvela
800 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON with Blue Box – MULTIPACK OF 180 (6 BOTTLES OF 30) TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Renvela 800 mg film-coated tablets
sevelamer carbonate

2. STATEMENT OF ACTIVE SUBSTANCE

Each tablet contains 800 mg sevelamer carbonate.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

180 (6 bottles of 30) film-coated tablets

5. METHOD AND ROUTE OF ADMINISTRATION

For oral use.
Tablets must be swallowed whole. Do not chew.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep bottle tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Genzyme Europe B.V.
Gooimeer 10
1411 DD Naarden
The Netherlands

12. MARKETING AUTHORISATION NUMBERS

EU/1/09/521/002 180 (6 bottles of 30) film-coated tablets

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Renvela
800 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON - CARTON OF 60 or 90 SACHETS

1. NAME OF THE MEDICINAL PRODUCT

Renvela 1.6 g powder for oral suspension
sevelamer carbonate

2. STATEMENT OF ACTIVE SUBSTANCE

Each sachet contains 1.6 g sevelamer carbonate.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for oral suspension
60 sachets
90 sachets

5. METHOD AND ROUTE OF ADMINISTRATION

For oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

8. EXPIRY DATE

EXP

The reconstituted suspension must be administered within 30 minutes of reconstitution.

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Genzyme Europe B.V.
Gooimeer 10
1411 DD Naarden
The Netherlands

12. MARKETING AUTHORISATION NUMBERS

EU/1/09/521/004
EU/1/09/521/005

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Renvela
1.6 g

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

LABEL - SACHETS

1. NAME OF THE MEDICINAL PRODUCT

Renvela 1.6 g powder for oral suspension
sevelamer carbonate

2. STATEMENT OF ACTIVE SUBSTANCE

Each sachet contains 1.6 g sevelamer carbonate.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for oral suspension

1.6 g powder

5. METHOD AND ROUTE OF ADMINISTRATION

For oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

8. EXPIRY DATE

EXP

The reconstituted suspension must be administered within 30 minutes of reconstitution.

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Genzyme Europe B.V.
Gooimeer 10
1411 DD Naarden
The Netherlands

12. MARKETING AUTHORISATION NUMBERS

EU/1/09/521/004
EU/1/09/521/005

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON - CARTON OF 60 or 90 SACHETS

1. NAME OF THE MEDICINAL PRODUCT

Renvela 2.4 g powder for oral suspension
sevelamer carbonate

2. STATEMENT OF ACTIVE SUBSTANCE

Each sachet contains 2.4 g sevelamer carbonate.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for oral suspension
60 sachets
90 sachets

5. METHOD AND ROUTE OF ADMINISTRATION

For oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

8. EXPIRY DATE

EXP

The reconstituted suspension must be administered within 30 minutes of reconstitution.

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Genzyme Europe B.V.
Gooimeer 10
1411 DD Naarden
The Netherlands

12. MARKETING AUTHORISATION NUMBERS

EU/1/09/521/006
EU/1/09/521/007

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Renvela
2.4 g

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

LABEL - SACHETS

1. NAME OF THE MEDICINAL PRODUCT

Renvela 2.4 g powder for oral suspension
sevelamer carbonate

2. STATEMENT OF ACTIVE SUBSTANCE

Each sachet contains 2.4 g sevelamer carbonate.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for oral suspension

2.4 g powder

5. METHOD AND ROUTE OF ADMINISTRATION

For oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

8. EXPIRY DATE

EXP

The reconstituted suspension must be administered within 30 minutes of reconstitution.

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Genzyme Europe B.V.
Gooimeer 10
1411 DD Naarden
The Netherlands

12. MARKETING AUTHORISATION NUMBERS

EU/1/09/521/006
EU/1/09/521/007

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Renvela 800 mg film-coated tablets
sevelamer carbonate

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have further questions, ask your doctor or your pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to you doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Renvela is and what it is used for

Renvela contains sevelamer carbonate as the active ingredient. It binds phosphate from food in the digestive tract and so reduces serum phosphorus levels in the blood.

Renvela is used to control hyperphosphataemia (high blood phosphate levels) 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 chronic (long-term) kidney disease who are not on dialysis and have a serum (blood) phosphorus level equal to or above 1.78 mmol/l.

Renvela should be used with other treatments such as calcium supplements and vitamin D to prevent the development of bone disease.
Increased levels of serum phosphorus can lead to hard deposits in your body called calcification. These deposits is can stiffen your blood vessels and make it harder for blood to be pumped around the body.
Increased serum phosphorus can also lead to itchy skin, red eyes, bone pain and fractures.

2. What you need to know before you take Renvela

Do not take Renvela if:
- you have low levels of phosphate in your blood (your doctor will check this for you)
- you have bowel obstruction
- you are allergic to the active substance or to any of the other ingredients of this medicine (listed in section 6).

Warnings and Precautions
Talk to your doctor before taking Renvela if any of the following applies to you:
- swallowing problems
- problems with motility (movement) in your stomach and bowel

- being sick frequently
- active inflammation of the bowel
- have undergone major surgery on your stomach or bowel.

Additional treatments:
Due to either your kidney condition or your dialysis treatment you may:

- develop low or high levels of calcium in your blood. Since Renvela does not contain calcium your doctor might prescribe additional calcium tablets.
- have a low amount of vitamin D in your blood. Therefore, your doctor may monitor the levels of vitamin D in your blood and prescribe additional vitamin D as necessary. If you do not take multivitamin supplements you may also develop low levels of vitamins A, E, K and folic acid in your blood and therefore your doctor may monitor these levels and prescribe supplemental vitamins as necessary.

Special note for patients on peritoneal dialysis:
You may develop peritonitis (infection of your abdominal fluid) associated with your peritoneal dialysis. This risk can be reduced by careful adherence to sterile techniques during bag changes. You should tell your doctor immediately if you experience any new signs or symptoms of abdominal distress, abdominal swelling, abdominal pain, abdominal tenderness, or abdominal rigidity, constipation, fever, chills, nausea or vomiting.
You should expect to be monitored more carefully for problems with low levels of vitamins A, D, E, K and folic acid.

Children
The safety and efficacy in children (below the age of 6 years) have not been studied. Therefore Renvela is not recommended for use in children below the age of 6 years.

Other medicines and Renvela
Tell your doctor if you are taking or have recently taken or might take any other medicines.

- Renvela should not be taken at the same time as ciprofloxacin (an antibiotic).

- If you are taking medicines for heart rhythm problems or for epilepsy, you should consult your doctor when taking Renvela.

- The effects of medicines such as ciclosporin, mycophenolate mofetil and tacrolimus (medicines used to suppress the immune system) may be reduced by Renvela. Your doctor will advise you if you are taking these medicines.

- Thyroid hormone deficiency may uncommonly be observed in certain people taking levothyroxine (used to treatment low thyroid hormone levels) and Renvela. Therefore your doctor may monitor the levels of thyroid stimulating hormone in your blood more closely.

- If you are taking medicine to treat heartburn, gastroesophageal reflux disease (GERD) or gastric ulcers, such as omeprazole, pantoprazole, or lansoprazole, you should consult your doctor when taking Renvela.

Your doctor will check for interactions between Renvela and other medicines on a regular basis.

In some cases where Renvela should be taken at the same time as another medicine. Your doctor may advise you to take this medicine 1 hour before or 3 hours after Renvela intake, or they may consider monitoring the blood levels of that medicine.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.
It is unknown whether Renvela has any affect on unborn babies.

Tell your doctor if you wish to breast-feed your baby. It is unknown whether Renvela may pass through breast milk and affect your baby.

Driving and using machines
Renvela is unlikely to affect your ability to drive or to use machines.

3. How to take Renvela

You must take Renvela as prescribed by your doctor. They will base the dose on your serum phosphorus level.

The recommended starting dose of Renvela tablets for adults and older people (> 65 years) is one to two tablets of 800 mg with each meal, 3 times a day.

The tablets must be swallowed whole. Do not crush, chew or break into pieces.

Initially, your doctor will check the levels of phosphorus in your blood every 2-4 weeks and may adjust the dose of Renvela when necessary to reach an adequate phosphate level.

Patients taking Renvela should adhere to their prescribed diets.

If you take more Renvela than you should
In the event of a possible overdose you should contact your doctor immediately.

If you forget to take Renvela
If you have missed one dose, this dose should be omitted and the next dose should be taken at the usual time with a meal. Do not take a double dose to make up for a forgotten dose.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Since constipation may be an early symptom of a blockage in your intestine, please inform your doctor or pharmacist.

The following side effects have been reported in patients taking Renvela:
Very common (may affect more than 1 in 10 people):
vomiting, constipation, upper abdominal pain, nausea

Common (may affect up to 1 in 10 people):
diarrhoea, abdominal pain, indigestion, flatulence

Very rare (may affect up to 1 in 10000 people):
hypersensitivity

Not known (frequency cannot be estimated from the available data):
cases of itching, rash, slow intestine motility (movement)/blockages in the intestine, and perforation in the intestine wall have been reported.

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Renvela

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date stated on the bottle and carton after the letters "EXP".

Keep the bottle container tightly closed in order to protect from moisture.
This medicinal product does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Renvela contains

- The active substance is sevelamer carbonate. Each Renvela film-coated tablet contains 800 mg of sevelamer carbonate
- The other ingredients are microcrystalline cellulose, sodium chloride and zinc stearate. The tablet coating contains hypromellose (E464) and diacetylated monoglycerides. The printing ink contains iron oxide black (E172), isopropyl alcohol, propylene glycol and hypromellose (E464).

What Renvela looks like and contents of the pack

Renvela film-coated tablets are white tablets with RENVELA 800 imprinted on one side. The tablets are packed in high density polyethylene bottles with a polypropylene cap and an induction seal.
Pack sizes:
1 x 30 tablets per bottle
1 x 180 tablets per bottle
180 tablets (6 bottles of 30 tablets)

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing authorisation holder:
Genzyme Europe B.V.
Gooimeer 10
1411 DD Naarden
The Netherlands

Manufacturer:
Genzyme Ltd.
37 Hollands Road
Haverhill, Suffolk
CB9 8PB
United Kingdom

Genzyme Ireland Ltd.
IDA Industrial Park
Old Kilmeaden Road
Waterford
Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation holder.

België/Belgique/Belgien/
Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: + 32 2 710 54 00

Lietuva
UAB „SANOFI-AVENTIS LIETUVA“
Tel. +370 5 275 5224

България
SANOFI BULGARIA EOOD
Тел: +359 2 9705300

Magyarország
SANOFI-AVENTIS Zrt
Tel: +36 1 505 0050

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Malta
Sanofi Malta Ltd
Tel: +356 21493022

Danmark
sanofi-aventis Denmark A/S
Tlf: +45 45 16 70 00

Nederland
sanofi-aventis Netherlands B.V.
Tel: +31 182 557 755

Deutschland
Sanofi-Aventis Deutschland GmbH
Tel: +49 (0)180 2 222010

Norge
sanofi-aventis Norge AS
Tlf: + 47 67 10 71 00

Eesti
sanofi-aventis Estonia OÜ
Tel. +372 6 273 488

Österreich
sanofi-aventis GmbH
Tel: + 43 1 80 185 - 0

Ελλάδα
sanofi-aventis AEBE
Τηλ: +30 210 900 1600

Polska
sanofi-aventis Sp. z o.o.
Tel.: +48 22 280 00 00

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

Portugal
Sanofi – Produtos Farmacêuticos, Lda..
Tel: +351 21 35 89 400

France
sanofi-aventis France
Tél : 0 800 222 555
Appel depuis l’étranger : +33 1 57 63 23 23

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Hrvatska
sanofi-aventis Croatia d.o.o.
Tel: +385 1 600 34 00

Slovenija
sanofi-aventis d.o.o.
Tel: +386 1 560 4800

Ireland
sanofi-aventis Ireland Ltd T/A SANOFI
Tel: +353 (0) 1 4035 600

Slovenská republika
sanofi-aventis Pharma Slovakia s.r.o.
Tel.: +421 2 33 100 100

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.p.A.
Tel: 800.536 389

Κύπρος
sanofi-aventis Cyprus Ltd.
Τηλ: +357 22 871600

Latvija
sanofi-aventis Latvia SIA
Tel: +371 67 33 24 51

Suomi/Finland
Sanofi Oy
Puh/Tel: + 358 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom
Sanofi
Tel: +44 (0) 845 372 7101

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

Package leaflet: Information for the user

Renvela 1.6 g powder for oral suspension
sevelamer carbonate

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have further questions, ask your doctor or your pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any of the side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Renvela is and what it is used for

Renvela contains sevelamer carbonate as the active ingredient. It binds phosphate from food in the digestive tract and so reduces serum phosphorus levels in the blood.

Renvela is used to control hyperphosphataemia (high blood phosphate levels) 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);
- adult patients with chronic (long-term) kidney disease who are not on dialysis and have a serum (blood) phosphorus level equal to or above 1.78 mmol/l.
- paediatric patients with chronic (long-term) kidney disease above the age of 6 and above a certain height and weight (used to calculate body surface area by your physician).

Renvela should be used with other treatments such as calcium supplements and vitamin D to prevent the development of bone disease.
Increased levels of serum phosphorus can lead to hard deposits in your body called calcification. These deposits is can stiffen your blood vessels and make it harder for blood to be pumped around the body. Increased serum phosphorus can also lead to itchy skin, red eyes, bone pain and fractures.

2. What you need to know before you take Renvela

Do not take Renvela if:
- you have low levels of phosphate in your blood (your doctor will check this for you)
- you have bowel obstruction
- you are allergic to the active substance or to any of the other ingredients of this medicine (listed in Section 6).

Warnings and precautions
Talk to you doctor before taking Renvela if any of the following applies to you:
- swallowing problems

- problems with motility (movement) in your stomach and bowel
- being sick frequently
- active inflammation of the bowel
- have undergone major surgery on your stomach or bowel.

Additional treatments:
Due to either your kidney condition or your dialysis treatment you may:

- develop low or high levels of calcium in your blood. Since Renvela does not contain calcium your doctor might prescribe additional calcium tablets.
- have a low amount of vitamin D in your blood. Therefore, your doctor may monitor the levels of vitamin D in your blood and prescribe additional vitamin D as necessary. If you do not take multivitamin supplements you may also develop low levels of vitamins A, E, K and folic acid in your blood and therefore your doctor may monitor these levels and prescribe supplemental vitamins as necessary.

Special note for patients on peritoneal dialysis:
You may develop peritonitis (infection of your abdominal fluid) associated with your peritoneal dialysis. This risk can be reduced by careful adherence to sterile techniques during bag changes. You should tell your doctor immediately if you experience any new signs or symptoms of abdominal distress, abdominal swelling, abdominal pain, abdominal tenderness, or abdominal rigidity, constipation, fever, chills, nausea or vomiting.
You should expect to be monitored more carefully for problems with low levels of vitamins A, D, E, K and folic acid.

Children
The safety and efficacy in children (below the age of 6 years) have not been studied. Therefore Renvela is not recommended for use in children below the age of 6 years.

Other medicines and Renvela
Tell your doctor if you are taking or have recently taken or might take any other medicines.

- Renvela should not be taken at the same time as ciprofloxacin (an antibiotic).

- If you are taking medicines for heart rhythm problems or for epilepsy, you should consult your doctor when taking Renvela.

- The effects of medicines such as ciclosporin, mycophenolate mofetil and tacrolimus (medicines used to suppress the immune system) may be reduced by Renvela. Your doctor will advise you if you are taking these medicines.

- Thyroid hormone deficiency may uncommonly be observed in certain people taking levothyroxine (used to treat low thyroid hormone levels) and Renvela. Therefore your doctor may monitor the levels of thyroid stimulating hormone in your blood more closely.

- If you are taking medicine to treat heartburn, gastroesophageal reflux disease (GERD) or gastric ulcers, such as omeprazole, prantoprazole, or lansoprazole, you should consult your doctor when taking Renvela.

Your doctor will check for interactions between Renvela and other medicines on a regular basis.

In some cases where Renvela should be taken at the same time as another medicine. Your doctor may advise you to take this medicine 1 hour before or 3 hours after Renvela intake, or they may consider monitoring the blood levels of that medicine.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. It is unknown whether Renvela has any affect on unborn babies.

Tell your doctor if you wish to breast-feed your baby. It is unknown whether Renvela may pass through breast milk and affect your baby.

Driving and using machines
Renvela is unlikely to affect your ability to drive or to use machines.

3. How to take Renvela

You must take Renvela as prescribed by your doctor. They will base the dose on your serum phosphorus level.

For a 1.6 g dose, the powder for oral suspension should be dispersed in 40 mL of water per sachet. Drink within 30 minutes of being prepared. It is important to drink all of the liquid and it may be necessary to rinse the glass with water and drink this as well to ensure that all of the powder is swallowed.

The recommended starting dose of Renvela for adults is 2.4-4.8g per day equally divided over three meals. The exact starting dose and regimen will be determined by your doctor.

Use in children and adolescents
The recommended starting dose of Renvela for children is based on their height and weight (used to calculate body surface area by your physician). For children, Renvela powder is preferred, as Renvela tablets are not appropriate in this population. Renvela should not be given on an empty stomach and should be taken with meals or snacks. The exact starting dose and regimen will be determined by your doctor.

For doses of less than 1.6 g, the Renvela powder in the sachet may be divided. The Renvela powder may be measured by volume (mL) using a measuring scoop or measuring spoon.

Sevelamer carbonate dose (g)	Volume (mL)
0.4 g (400 mg)	1.0 mL
0.8 g (800 mg)	2.0 mL
1.2 g (1200 mg)	3.0 mL
1.6 g (1600 mg)	4.0 mL

Preparation using a 1 mL measuring scoop:

For a 0.4 g dose:

- Open the sachet with scissors along the marked line.
- Insert the scoop into the sachet.
- Fill the scoop above the top edge.
- Withdraw the scoop from the sachet using the top edge of the open sachet to level the powder with the top of the scoop. This allows excess Renvela powder to fall back into the sachet.
- Disperse the 1.0 mL of the Renvela powder from the measuring scoop in 40 mL of water. Drink within 30 minutes of being prepared. It is important to drink all of the liquid and it may be necessary to rinse the glass with water and drink this as well to ensure that all of the powder is swallowed.
- Close the sachet by folding over twice.
- The remaining Renvela powder may be used within 24 hours for the next dose.

- Discard sachets of Renvela powder that have been opened for more than 24 hours.

◦ For a 0.8 g dose:
- Follow the instructions above, filling the scoop twice for a total of 2.0 mL Renvela powder.

For a 1.2 g dose:
- Follow the instructions above, filling the scoop three times for a total of 3.0 mL Renvela powder.

Preparation using a measuring spoon

For a 0.4 g dose:
- Open the sachet with scissors along the marked line.
- Hold the measuring spoon vertically.
- Pour the contents of the sachet into the measuring spoon to fill the spoon to 1.0 mL.
- Do not tap the dosing spoon to compact the powder.
- Disperse the 1.0 mL of the Renvela powder from the measuring spoon in 40 mL of water. Drink within 30 minutes of being prepared. It is important to drink all of the liquid and it may be necessary to rinse the glass with water and drink this as well to ensure that all of the powder is swallowed.
- Close the sachet by folding over twice.
- The remaining Renvela powder may be used within 24 hours for the next dose.
- Discard sachets of Renvela powder that have been opened for more than 24 hours.

For a 0.8 g dose:
- Follow the instructions above, filling the spoon twice for a total of 2.0 mL Renvela powder.

For a 1.2 g dose:
- Follow the instructions above, filling the spoon three times for a total of 3.0 mL Renvela powder.

Initially, your doctor will check the levels of phosphorus in your blood every 2-4 weeks and may adjust the dose of Renvela when necessary to reach an adequate phosphate level.

Patients taking Renvela should adhere to their prescribed diets.

If you take more Renvela than you should
In the event of a possible overdose you should contact your doctor immediately.

If you forget to take Renvela
If you have missed one dose, this dose should be omitted and the next dose should be taken at the usual time with a meal. Do not a double dose to make up for a forgotten dose.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Since constipation may be an early symptom of a blockage in your intestine, please inform your doctor or pharmacist.

The following side effects have been reported in patients taking Renvela:
Very common (may affect more than 1 in 10 people):
vomiting, constipation, upper abdominal pain, nausea

Common (may affect up to 1 in 10 people):
diarrhoea, abdominal pain, indigestion, flatulence

Very rare (may affect up to 1 in 10000 people):
hypersensitivity

Not known (frequency cannot be estimated from the available data):
cases of itching, rash, slow intestine motility (movement)/blockages in the intestine, and perforation in the intestine wall have been reported.

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Renvela

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date stated on the sachet and carton after the letters "EXP". The reconstituted suspension must be administered within 30 minutes of reconstitution.

The medicinal product does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Renvela contains

- The active substance is sevelamer carbonate. Each Renvela sachet contains 1.6 g of sevelamer carbonate.
- The other ingredients are propylene glycol alginate, citrus cream flavour, sodium chloride, sucralose and iron oxide yellow (E172).

What Renvela looks like and contents of the pack

Renvela powder for oral suspension is a pale yellow powder supplied in a foil sachet with a heat seal. The foil sachets are packaged in an outer carton.

Pack sizes:
60 sachets per carton
90 sachets per carton

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing authorisation holder:
Genzyme Europe B.V.
Gooimeer 10
1411 DD Naarden
The Netherlands

Manufacturer:
Genzyme Ltd.
37 Hollands Road
Haverhill, Suffolk
CB9 8PB
United Kingdom

Genzyme Ireland Ltd.
IDA Industrial Park
Old Kilmeaden Road
Waterford
Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation holder.

België/Belgique/Belgien/
Luxembourg Luxemburg
Sanofi Belgium
Tél/Tel: + 32 2 710 54 00

Lietuva
UAB „SANOFI-AVENTIS LIETUVA“
Tel. +370 5 275 5224

България
SANOFI BULGARIA EOOD
Тел: +359 2 9705300

Magyarország
SANOFI-AVENTIS Zrt
Tel: +36 1 505 0050

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Malta
Sanofi Malta Ltd
Tel: +356 21493022

Danmark
sanofi-aventis Denmark A/S
Tlf: +45 45 16 70 00

Nederland
sanofi-aventis Netherlands B.V.
Tel: +31 182 557 755

Deutschland
Sanofi-Aventis Deutschland GmbH
Tel: +49 (0)180 2 222010

Norge
sanofi-aventis Norge AS
Tlf: + 47 67 10 71 00

Eesti
sanofi-aventis Estonia OÜ
Tel. +372 6 273 488

Österreich
sanofi-aventis GmbH
Tel: + 43 1 80 185 - 0

Ελλάδα
sanofi-aventis AEBE
Τηλ: +30 210 900 1600

Polska
sanofi-aventis Sp. z o.o.
Tel.: +48 22 280 00 00

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

Portugal
Sanofi – Produtos Farmacêuticos, Lda..
Tel: +351 21 35 89 400

France
sanofi-aventis France
Tél : 0 800 222 555
Appel depuis l’étranger : +33 1 57 63 23 23

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Hrvatska
sanofi-aventis Croatia d.o.o.

Slovenija
sanofi-aventis d.o.o.

Tel: +385 1 600 34 00

Ireland
sanofi-aventis Ireland Ltd T/A SANOFI
Tel: +353 (0) 1 4035 600

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.p.A.
Tel: 800.536 389

Κύπρος
sanofi-aventis Cyprus Ltd.
Τηλ: +357 22 871600

Latvija
sanofi-aventis Latvia SIA
Tel: +371 67 33 24 51

Tel: +386 1 560 4800

Slovenská republika
sanofi-aventis Pharma Slovakia s.r.o.
Tel.: +421 2 33 100 100

Suomi/Finland
Sanofi Oy
Puh/Tel: + 358 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom
Sanofi
Tel: +44 (0) 845 372 7101

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

Package leaflet: Information for the user

Renvela 2.4 g powder for oral suspension
sevelamer carbonate

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have further questions, ask your doctor or your pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Renvela is and what it is used for

Renvela contains sevelamer carbonate as the active ingredient. It binds phosphate from food in the digestive tract and so reduces serum phosphorus levels in the blood.

Renvela is used to control hyperphosphataemia (high blood phosphate levels) 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);
- adult patients with chronic (long-term) kidney disease who are not on dialysis and have a serum (blood) phosphorus level equal to or above 1.78 mmol/l.
- paediatric patients with chronic (long-term) kidney disease above the age of 6 and above a certain height and weight (used to calculate body surface area by your physician).

Renvela should be used with other treatments such as calcium supplements and vitamin D to prevent the development of bone disease.
Increased levels of serum phosphorus can lead to hard deposits in your body called calcification. These deposits can stiffen your blood vessels and make it harder for blood to be pumped around the body. Increased serum phosphorus can also lead to itchy skin, red eyes, bone pain and fractures.

2. What you need to know before you take Renvela

Do not take Renvela if:
- you have low levels of phosphate in your blood (your doctor will check this for you)
- you have bowel obstruction
- you are allergic to the active substance or to any of the other ingredients of this medicine (listed in Section 6).

Warnings and Precautions
Talk to your doctor before taking Renvela if any of the following applies to you:
- swallowing problems

- problems with motility (movement) in your stomach and bowel
- being sick frequently
- active inflammation of the bowel
- have undergone major surgery on your stomach or bowel.

Additional treatments:
Due to either your kidney condition or your dialysis treatment you may:

- develop low or high levels of calcium in your blood. Since Renvela does not contain calcium your doctor might prescribe additional calcium tablets.
- have a low amount of vitamin D in your blood. Therefore, your doctor may monitor the levels of vitamin D in your blood and prescribe additional vitamin D as necessary. If you do not take multivitamin supplements you may also develop low levels of vitamins A, E, K and folic acid in your blood and therefore your doctor may monitor these levels and prescribe supplemental vitamins as necessary.

Special note for patients on peritoneal dialysis:
You may develop peritonitis (infection of your abdominal fluid) associated with your peritoneal dialysis. This risk can be reduced by careful adherence to sterile techniques during bag changes. You should tell your doctor immediately if you experience any new signs or symptoms of abdominal distress, abdominal swelling, abdominal pain, abdominal tenderness, or abdominal rigidity, constipation, fever, chills, nausea or vomiting.
You should expect to be monitored more carefully for problems with low levels of vitamins A, D, E, K and folic acid.

Children
The safety and efficacy in children (below the age of 6 years) have not been studied. Therefore Renvela is not recommended for use in children below the age of 6 years.

Other medicines and Renvela
Tell your doctor if you are taking or have recently taken or might take any other medicines.

- Renvela should not be taken at the same time as ciprofloxacin (an antibiotic).

- If you are taking medicines for heart rhythm problems or for epilepsy, you should consult your doctor when taking Renvela.

- The effects of medicines such as ciclosporin, mycophenolate mofetil and tacrolimus (medicines used to suppress the immune system) may be reduced by Renvela. Your doctor will advise you if you are taking these medicines.

- Thyroid hormone deficiency may uncommonly be observed in certain people taking levothyroxine (used to treat low thyroid hormone levels) and Renvela. Therefore your doctor may monitor the levels of thyroid stimulating hormone in your blood more closely.

- If you are taking medicine to treat heartburn, gastroesophageal reflux disease (GERD) or gastric ulcers, such as omeprazole, pantoprazole, or lansoprazole, you should consult your doctor when taking Renvela.

Your doctor will check for interactions between Renvela and other medicines on a regular basis.

In some cases where Renvela should be taken at the same time as another medicine. Your doctor may advise you to take this medicine 1 hour before or 3 hours after Renvela intake, or they may consider monitoring the blood levels of that medicine.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advise before taking this medicine. It is unknown whether Renvela has any affect on unborn babies.

Tell your doctor if you wish to breast-feed your baby. It is unknown whether Renvela may pass through breast milk and affect your baby.

Driving and using machines
Renvela is unlikely to affect your ability to drive or to use machines.

3. How to take Renvela

You must take Renvela as prescribed by your doctor. They will base the dose on your serum phosphorus level.

For a 2.4 g dose, the powder for oral suspension should be dispersed in 60 mL of water per sachet. Drink within 30 minutes of being prepared. It is important to drink all of the liquid and it may be necessary to rinse the glass with water and drink this as well to ensure that all of the powder is swallowed.

The recommended starting dose of Renvela for adults is 2.4-4.8 g per day equally divided over three meals. The exact starting dose and regimen will be determined by your doctor.

Use in children and adolescents
The recommended starting dose of Renvela for children is based on their height and weight (used to calculate body surface area by your physician). For children, Renvela powder is preferred, as Renvela tablets are not appropriate in this population. Renvela should not be given on an empty stomach and should be taken with meals or snacks. The exact starting dose and regimen will be determined by your doctor.

For doses of less than 2.4 g, the Renvela powder in the sachet may be divided. The Renvela powder may be measured by volume (mL) using a measuring scoop or measuring spoon.

Sevelamer carbonate dose (g)	Volume (mL)
0.4 g (400 mg)	1.0 mL
0.8 g (800 mg)	2.0 mL
1.2 g (1200 mg)	3.0 mL
1.6 g (1600 mg)	4.0 mL

Preparation using a 1 mL measuring scoop:

For a 0.4 g dose:

- Open the sachet with scissors along the marked line.
  - Insert the scoop into the sachet.
  - Fill the scoop above the top edge.
  - Withdraw the scoop from the sachet using the top edge of the open sachet to level the powder with the top of the scoop. This allows excess Renvela powder to fall back into the sachet.
- Disperse the 1.0 mL of the Renvela powder from the measuring scoop in 60 mL of water. Drink within 30 minutes of being prepared. It is important to drink all of the liquid and it may be necessary to rinse the glass with water and drink this as well to ensure that all of the powder is swallowed.
- Close the sachet by folding over twice.

- The remaining Renvela powder may be used within 24 hours for the next dose.
- Discard sachets of Renvela powder that have been opened for more than 24 hours.

For a 0.8 g dose:
- Follow the instructions above, filling the scoop twice for a total of 2.0 mL Renvela powder.

For a 1.2 g dose:
- Follow the instructions above, filling the scoop three times for a total of 3.0 mL Renvela powder.

For a 1.6 g dose:
- Follow the instructions above, filling the scoop four times for a total of 4.0 mL Renvela powder.

Preparation using a measuring spoon

For a 0.4 g dose:
- Open the sachet with scissors along the marked line.
- Hold the measuring spoon vertically.
- Pour the contents of the sachet into the measuring spoon to fill the spoon to 1.0 mL.
- Do not tap the dosing spoon to compact the powder.
- Disperse the 1.0 mL of the Renvela powder from the measuring spoon in 60 mL of water. Drink within 30 minutes of being prepared. It is important to drink all of the liquid and it may be necessary to rinse the glass with water and drink this as well to ensure that all of the powder is swallowed.
- Close the sachet by folding over twice.
- The remaining Renvela powder may be used within 24 hours for the next dose.
- Discard sachets of Renvela powder that have been opened for more than 24 hours.

For a 0.8 g dose:
- Follow the instructions above, filling the spoon twice for a total of 2.0 mL Renvela powder.

For a 1.2 g dose:
- Follow the instructions above, filling the spoon three times for a total of 3.0 mL Renvela powder.

For a 1.6 g dose:
- Follow the instructions above, filling the spoon four times for a total of 4.0 mL Renvela powder.

Initially, your doctor will check the levels of phosphorus in your blood every 2-4 weeks and they may adjust the dose of Renvela when necessary to reach an adequate phosphate level.

Patients taking Renvela should adhere to their prescribed diets.

If you take more Renvela than you should
In the event of a possible overdose you should contact your doctor immediately.

If you forget to take Renvela
If you have missed one dose, this dose should be omitted and the next dose should be taken at the usual time with a meal. Do not a double dose to make up for a forgotten dose.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Since constipation may be an early symptom of a blockage in your intestine, please inform your doctor or pharmacist.

The following side effects have been reported in patients taking Renvela:
Very common (may affect more than 1 in 10 people):
vomiting, constipation, upper abdominal pain, nausea

Common (may affect up to 1 in 10 people):
diarrhoea, abdominal pain, indigestion, flatulence

Very rare (may affect up to 1 in 10000 people):
hypersensitivity

Not known (frequency cannot be estimated from the available data):
cases of itching, rash, slow intestine motility (movement)/blockages in the intestine, and perforation in the intestine wall have been reported.

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Renvela

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date stated on the sachet and carton after the letters "EXP". The reconstituted suspension must be administered within 30 minutes of reconstitution.

The medicinal product does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Renvela contains

- The active substance is sevelamer carbonate. Each Renvela sachet contains 2.4 g of sevelamer carbonate.
- The other ingredients are propylene glycol alginate, citrus cream flavour, sodium chloride, sucralose and iron oxide yellow (E172).

What Renvela looks like and contents of the pack

Renvela powder for oral suspension is a pale yellow powder supplied in a foil sachet with a heat seal. The foil sachets are packaged in an outer carton.

Pack sizes:
60 sachets per carton
90 sachets per carton

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing authorisation holder:
Genzyme Europe B.V.
Gooimeer 10
1411 DD Naarden
The Netherlands

Manufacturer:
Genzyme Ltd.
37 Hollands Road
Haverhill, Suffolk
CB9 8PB
United Kingdom

Genzyme Ireland Ltd.
IDA Industrial Park
Old Kilmeaden Road
Waterford
Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation holder.

België/Belgique/Belgien/
Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: + 32 2 710 54 00

България
SANOFI BULGARIA EOOD
Тел: +359 2 9705300

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Danmark
sanofi-aventis Denmark A/S
Tlf: +45 45 16 70 00

Deutschland
Sanofi-Aventis Deutschland GmbH
Tel: +49 (0)180 2 222010

Eesti
sanofi-aventis Estonia OÜ
Tel. +372 6 273 488

Ελλάδα
sanofi-aventis AEBE
Τηλ: +30 210 900 1600

Lietuva
UAB „SANOFI-AVENTIS LIETUVA“
Tel. +370 5 275 5224

Magyarország
SANOFI-AVENTIS Zrt
Tel: +36 1 505 0050

Malta
Sanofi Malta Ltd
Tel: +356 21493022

Nederland
sanofi-aventis Netherlands B.V.
Tel: +31 182 557 755

Norge
sanofi-aventis Norge AS
Tlf: + 47 67 10 71 00

Österreich
sanofi-aventis GmbH
Tel: + 43 1 80 185 - 0

Polska
sanofi-aventis Sp. z o.o.
Tel.: +48 22 280 00 00

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

France
sanofi-aventis France
Tél : 0 800 222 555
Appel depuis l'étranger : +33 1 57 63 23 23

Hrvatska
sanofi-aventis Croatia d.o.o.
Tel: +385 1 600 34 00

Ireland
sanofi-aventis Ireland Ltd T/A SANOFI
Tel: +353 (0) 1 4035 600

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.p.A.
Tel: 800.536 389

Κύπρος
sanofi-aventis Cyprus Ltd.
Τηλ: +357 22 871600

Latvija
sanofi-aventis Latvia SIA
Tel: +371 67 33 24 51

Portugal
Sanofi – Produtos Farmacêuticos, Lda..
Tel: +351 21 35 89 400

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
sanofi-aventis d.o.o.
Tel: +386 1 560 4800

Slovenská republika
sanofi-aventis Pharma Slovakia s.r.o.
Tel.: +421 2 33 100 100

Suomi/Finland
Sanofi Oy
Puh/Tel: + 358 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom
Sanofi
Tel: +44 (0) 845 372 7101

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.