

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Renagel 800 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 800 mg sevelamer hydrochloride.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Off-white oval and film-coated tablet, engraved with “RG800” on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Renagel is indicated for the control of hyperphosphataemia in adult patients receiving haemodialysis or peritoneal dialysis. Renagel should be used within the context of a multiple therapeutic approach, which could include calcium supplements, 1,25-dihydroxy Vitamin D₃ 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 hydrochloride is 2.4 g or 4.8 g per day based on clinical needs and serum phosphorus level. Renegel must be taken three times per day with meals.

Serum phosphate level in patients not on phosphate binders	Starting dose of Renegel 800 mg tablets
1.76 – 2.42 mmol/L (5.5 – 7.5 mg/dl)	1 tablet, 3 times per day
> 2.42 mmol/L (>7.5 mg/dl)	2 tablets, 3 times per day

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

Titration and maintenance

Serum phosphate levels should be closely monitored and the dose of sevelamer hydrochloride titrated by 0.8 g three times per day (2.4 g/day) increments with the goal of lowering serum phosphate to 1.76 mmol/L (5.5 mg/dl) or less. Serum phosphate should be tested every two to three weeks until a stable serum phosphate level is reached and on a regular basis thereafter.

The dose range may vary between 1 and 5 tablets of 800 mg per meal. The average actual daily dose used in the chronic phase of a one year clinical study was 7 g of sevelamer.

Paediatric population

The safety and efficacy of this product have not been established in patients below the age of 18 years.

Renal impairment

The safety and efficacy of this product have not been established in predialysis patients.

Method of administration

For oral use

Patients should take Renegel with meals and adhere to their prescribed diets. The tablets must be swallowed whole. Do not crush, chew or break into pieces prior to administration.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Efficacy and safety of Renegel has not been studied in patients with:

- swallowing disorders

- active inflammatory bowel disease
- gastrointestinal motility disorders including untreated or severe gastroparesis, diverticulosis retention of gastric contents and abnormal or irregular bowel motion
- patients with a history of major gastrointestinal surgery

Therefore caution should be exercised when Renagel is used in patients with these disorders.

Intestinal obstruction and ileus/subileus

In very rare cases, intestinal obstruction and ileus/subileus have been observed in patients during treatment with sevelamer hydrochloride. Constipation may be a preceding symptom. Patients who are constipated should be monitored carefully while being treated with sevelamer hydrochloride. Renagel treatment should be re-evaluated in patients who develop severe constipation or other severe gastrointestinal symptoms.

Fat-soluble vitamins

Depending on diet intake and the nature of end stage renal failure, dialysis patients may develop low vitamin A, D, E and K levels. It cannot be excluded that Renagel can bind fat-soluble vitamins contained in ingested food. Therefore, in patients not taking these vitamins, monitoring vitamin A, D and E levels and assessing vitamin K status through the measurement of thromboplastin time should be considered and the vitamins should be supplemented if necessary. Additional monitoring of vitamins and folic acid is recommended in patients receiving peritoneal dialysis, since in the clinical study, vitamin A, D, E and K levels were not measured in these patients.

Folate deficiency

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

Hypocalcaemia/hypercalcaemia

Patients with renal insufficiency may develop hypocalcaemia or hypercalcaemia. Renagel does not contain calcium. Serum calcium levels should be monitored as is done in normal follow-up of a dialysis patient. Elemental calcium should be given as a supplement in case of hypocalcaemia.

Metabolic acidosis

Patients with chronic renal failure are predisposed to developing metabolic acidosis. Worsening of acidosis has been reported upon switching from other phosphate binders to sevelamer in a number of studies where lower bicarbonate levels in the sevelamer-treated patients compared to patients treated with calcium-based binders were observed. Closer monitoring of serum bicarbonate levels is therefore recommended.

Peritonitis

Patients receiving dialysis are subject to certain risks for infection specific to the dialysis modality. Peritonitis is a known complication in patients receiving peritoneal dialysis (PD) and in a clinical study with Renagel, a number of peritonitis cases were reported. Therefore, patients on PD should be closely monitored to ensure the reliable 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 Renagel 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 Renagel is used in patients with difficulty swallowing.

Hypothyroidism

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

Long term chronic treatment

As data on the chronic use of sevelamer for over one year are not yet available, potential absorption and accumulation of sevelamer during long-term chronic treatment cannot be totally excluded (see section 5.2).

Hyperparathyroidism

Renagel alone is not indicated for the control of hyperparathyroidism. In patients with secondary hyperparathyroidism Renagel should be used within the context of a multiple therapeutic approach, which could include calcium supplements, 1,25-dihydroxy Vitamin D₃ or one of its analogues to lower the intact parathyroid hormone (iPTH) levels.

Serum chloride

Serum chloride may increase during Renagel treatment as chloride may be exchanged for phosphorus in the intestinal lumen. Although no clinically significant serum chloride increase has been observed in the clinical studies, serum chloride should be monitored as is done in the routine follow-up of a dialysis patient. One gram of Renagel contains approximately 180 mg (5.1 mEq) chloride.

Inflammatory Gastrointestinal Disorders

Cases of serious inflammatory disorders of different parts of the gastrointestinal tract (including serious complications such as haemorrhage, perforation, ulceration, necrosis, colitis and colonic/caecal mass) associated with the presence of sevelamer crystals have been reported (see section 4.8). Inflammatory disorders may resolve upon sevelamer discontinuation. Sevelamer hydrochloride 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 decreased the bioavailability of ciprofloxacin by approximately 50% when co-administered with Renagel in a single dose study. Consequently, Renagel should not be taken simultaneously with ciprofloxacin.

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 sevelamer hydrochloride to patients also taking these medicinal products.

Levothyroxine

During post marketing experience, very rare cases of increased thyroid stimulating hormone (TSH) levels have been reported in patients co-administered sevelamer hydrochloride and levothyroxine. Closer monitoring of TSH levels is therefore recommended in patients receiving both medicinal products.

Ciclosporin, mycophenolate mofetil and tacrolimus in transplant patients

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

Digoxin, warfarin, enalapril or metoprolol

In interaction studies in healthy volunteers, Renagel 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 hydrochloride.

Bioavailability

Renagel 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 Renagel, or the physician should consider monitoring blood levels.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of sevelamer hydrochloride has not been established in pregnant women. In animal studies there was no evidence that sevelamer induced embryo-fetal toxicity. Renagel 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 fetus (see section 5.3).

Breast-feeding

The safety of sevelamer hydrochloride has not been established in breast-feeding women. Renagel should only be given to breast-feeding women if clearly needed and after a careful risk/benefit analysis has been conducted for both the mother and the infant (see section 5.3).

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 ($\geq 5\%$ of patients) adverse reactions were all in the gastrointestinal disorders system organ class.

Tabulated list of adverse reactions

In parallel design studies involving 244 haemodialysis patients with treatment duration of up to 54 weeks and 97 peritoneal dialysis patients with treatment duration of 12 weeks were conducted.

Adverse reactions from these studies (299 patients), from uncontrolled clinical trials (384 patients), and that were spontaneously reported from post-marketing experience are listed by frequency in the table below. The reporting rate is classified as very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ 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	Uncommon	Very Rare	Not known
Immune system disorders				Hypersensitivity*	
Metabolism			Acidosis,		

and nutrition disorders			increased serum chloride levels		
Gastrointestinal disorders	Nausea, vomiting	Diarrhoea, dyspepsia, flatulence, upper abdominal pain, constipation			Abdominal pain, intestinal obstruction, ileus/sub-ileus, diverticulitis, intestinal perforation ¹ , gastrointestinal haemorrhage* ¹ , intestinal ulceration* ¹ , gastrointestinal necrosis* ¹ , colitis* ¹ , intestinal mass* ¹
Skin and subcutaneous tissue disorders					Pruritus, rash
Investigations					Crystal deposit intestine* ¹

**post-marketing experience*

¹ See inflammatory gastrointestinal disorders warning in section 4.4.

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Renagel has been given to normal healthy volunteers in doses up to 14 g, the equivalent of seventeen 800 mg tablets per day for eight days with no undesirable effects.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Treatment of hyperphosphataemia. ATC code: V03AE02.

Renagel contains sevelamer, a non-absorbed phosphate binding poly-(allylamine hydrochloride) polymer, free of metal and calcium. It contains multiple amines separated by one carbon from the polymer backbone. These amines become partially protonated in the intestine and interact with phosphate molecules through ionic and hydrogen bonding. By binding phosphate in the gastrointestinal tract, sevelamer lowers the phosphate concentration in the serum.

In clinical trials, sevelamer has been shown to be effective in reducing serum phosphorus in patients receiving haemodialysis or peritoneal dialysis.

Sevelamer decreases the incidence of hypercalcaemic episodes as compared to patients using calcium-based phosphate binders alone, probably because the product itself does not contain calcium. The effects on phosphate and calcium were proven to be maintained throughout a study with one year follow-up.

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 mean total and LDL cholesterol declined by 15—31%. This effect is observed after 2 weeks is maintained with long-term treatment. Triglycerides, HDL cholesterol and albumin did not change.

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 Renagel should be used within the context of a multiple therapeutic approach, which could include calcium supplements, 1,25-dihydroxy Vitamin D₃ or one of its analogues to lower the iPTH levels.

In a clinical trial of one-year duration, Renagel had no adverse effect on bone turnover or mineralisation compared to calcium carbonate.

5.2 Pharmacokinetic properties

Renagel is not absorbed from the gastrointestinal tract according to a single dose pharmacokinetic study in healthy volunteers. Pharmacokinetic studies have not been carried out in renal failure patients (see section 4.4).

5.3 Preclinical safety data

In preclinical studies in rats and dogs, Renagel at a dose of 10 times the maximum human doses reduced absorption of fat-soluble vitamins D, E and K, and folic acid.

In a study in rats, administering sevelamer in 15 – 30 x the human dose, an increase in serum copper was detected. This was not confirmed in a dog study or in clinical trials. *Currently, no formal carcinogenicity data are available. However, in vitro and in vivo studies have indicated that Renagel does not have genotoxic potential. Also, the medicinal product is not absorbed in the gastrointestinal tract.*

In reproduction studies there was no evidence that sevelamer induced embryo-lethality, fetotoxicity or teratogenicity at the doses tested (up to 1 g/kg/day in rabbits and up to 4.5 g/kg/day in rats). Deficits in skeletal ossification were observed in several locations in fetuses of female rats dosed with sevelamer at 8–20 times the maximum human dose of 200 mg/kg. The effects may be secondary to vitamin D and/or vitamin K depletion at these high doses.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Silica, colloidal anhydrous

Stearic acid

Film-coating:

Hypromellose (E464)

Diacetylated monoglycerides

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C.

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

6.5 Nature and contents of container

HDPE bottles, with a child resistant polypropylene closure and a foil induction seal.

Package sizes are:

1 bottle of 100 film-coated tablets

1 bottle of 180 film-coated tablets

multipacks containing 180 film-coated tablets (6 bottles of 30 tablets)

multipacks containing 360 film-coated tablets (2 bottles of 180 tablets)

multipacks containing 540 film-coated tablets (3 bottles of 180 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

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PLGB 04425/0772

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AUTHORISATION**

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25/09/2023