SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Sevelamer Hydrochloride 800 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 800 mg sevelamer hydrochloride.

Excipients with known effect: This medicine contains 96 mg sorbitol in each tablet.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet)

White to off-white oval shape film coated tablet having approx. 19.10 x 9.80 mm dimension, debossed with 800 on one side and debossed with SH on other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Serum phosphate level in patients not on phosphate binders	Starting dose of Sevelamer Hydrochloride 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, Sevelamer Hydrochloride 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 grams 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 Sevelamer Hydrochloride 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 Sevelamer Hydrochloride 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 Sevelamer Hydrochloride 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. Sevelamer Hydrochloride 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 Sevelamer Hydrochloride 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 Sevelamer Hydrochloride treatment.

Hypocalcaemia/hypercalcaemia

Patients with renal insufficiency may develop hypocalcaemia or hypercalcaemia. Sevelamer Hydrochloride 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 Sevelamer Hydrochloride, 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 Sevelamer hydrochloride 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 Sevelamer Hydrochloride 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
Sevelamer Hydrochloride alone is not indicated for the control of hyperparathyroidism. In patients with secondary hyperparathyroidism Sevelamer Hydrochloride should be used within the context of a multiple therapeutic approach, which could include calcium supplements, 1,25-dihydroxy Vitamin D_3 or one of its analogues to lower the intact parathyroid hormone (iPTH) levels.

Serum chloride
Serum chloride may increase during Sevelamer Hydrochloride 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 Sevelamer Hydrochloride 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 bleeding, 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.

Excipient warnings in the formulation
Sevelamer Hydrochloride tablets contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

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 Sevelamer Hydrochloride in a single dose study. Consequently, Sevelamer Hydrochloride 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, Sevelamer Hydrochloride 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
Sevelamer Hydrochloride 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 Sevelamer Hydrochloride, 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-foetal toxicity. Sevelamer Hydrochloride 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 (see section 5.3).

Breast-feeding
The safety of sevelamer hydrochloride has not been established in breast-feeding women. Sevelamer Hydrochloride 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 (≥5% of patients) adverse reactions were all in the gastrointestinal disorders system organ class.

Tabulated list of adverse reactions

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 (≥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 form the available data).

MedDRA System Organ Class	Very Common	Common	Uncommon	Very Rare	Not known
Immune system disorders				Hypersensitivity *	
Metabolism and nutrition disorders			Acidosis, increased serum chloride levels		
Gastrointestinal disorders	Nausea, vomiting	Diarrhoea, dyspepsia, flatulence, upper abdominal pain, constipation			Abdominal pain, intestinal obstruction, ileus/subileus, diverticulitis, intestinal Perforation[1] gastrointestinal[1] hemorrhage*[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

Sevelamer Hydrochloride has been given to normal healthy volunteers in doses up to 14 grams, 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 hyperphosphatemia. ATC code: V03AE02.

Sevelamer Hydrochloride 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 Sevelamer Hydrochloride should be used within the context of a multiple therapeutic approach, which could include calcium supplements, 1,25-dihydroxy Vitamin D_3 or one of its analogues to lower the iPTH levels.

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

5.2 Pharmacokinetic properties

Sevelamer Hydrochloride 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, Sevelamer Hydrochloride 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 Sevelamer Hydrochloride 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 embryolethality, foetotoxicity 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:
Sorbitol (E 420)
Hypromellose (E 464)
Crosspovidone type B
Silica, colloidal anhydrous
Magnesium stearate

Film-coating:
Opadry white 20F580006 contains;
Hypromellose (E 464)
Hydroxypropyl cellulose (E 463)
Macrogol 6000 (E 1521)
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

The HDPE bottles containing silica gel desiccant with a child resistant polypropylene closure and an induction seal.
Pack sizes are:
1 bottle of 30 film-coated tablets
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

Waymade PLC
Sovereign House, Miles Gray Road,
Basildon, Essex, SS14 3FR
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 06464/3112

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22/04/2025

10 DATE OF REVISION OF THE TEXT

22/04/2025