**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Sevelamer carbonate Winthrop 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).
White to off-white oval tablet, engraved with "RV800" on one side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

Sevelamer carbonate Winthrop is also indicated for the control of hyperphosphataemia in adult patients with chronic kidney disease (CKD) not on dialysis with serum phosphorus ≥ 1.78 mmol/L.

Sevelamer carbonate Winthrop 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. Sevelamer carbonate Winthrop 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, see section "Titration and maintenance"

For patients previously on phosphate binders (sevelamer hydrochloride or calcium based), Sevelamer carbonate Winthrop 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 Sevelamer carbonate Winthrop should adhere to their prescribed diets.

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

Special populations

*Elderly population*
No dosage adjustment is necessary in the elderly population.

*Hepatic impairment*
No studies have been performed in patients with hepatic impairment.

*Paediatric population*
The safety and efficacy of Sevelamer carbonate Winthrop in children below the age of 6 years or in children with a BSA (Body Surface Area) below 0.75 $m^2$ have not been established. No data are available.

The safety and efficacy of Sevelamer carbonate Winthrop in children over 6 year of age and a BSA >0.75 $m^2$ have been established. Current available data are described in section 5.1.

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

Method of administration

Oral use.
Tablets should be swallowed intact and should not be crushed, chewed, or broken into pieces prior to administration.
Sevelamer carbonate Winthrop 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 sevelamer carbonate have not been established in adult patients with chronic kidney disease not on dialysis with serum phosphorus < 1.78 mmol/L. Therefore it is currently not recommended for use in these patients.

The safety and efficacy of sevelamer carbonate 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

Treatment of these patients with Sevelamer carbonate Winthrop should only be initiated after careful benefit/risk assessment. If the therapy is initiated, patients suffering from these disorders should be monitored. Sevelamer carbonate treatment should be reevaluated in patients who develop severe constipation or other severe gastrointestinal symptoms.

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 sevelamer carbonate. The treatment should be re-evaluated in patients who develop severe constipation or other severe gastrointestinal symptoms.

Fat-soluble vitamins and folate deficiency

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 sevelamer carbonate 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 sevelamer carbonate. In patients undergoing peritoneal dialysis additional monitoring of fat-soluble vitamins and folic acid is recommended, since vitamin A, D, E and K levels were not measured in a clinical study in these patients.

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

Hypocalcaemia/hypercalcaemia

Patients with CKD may develop hypocalcaemia or hypercalcaemia. 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 CKD 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 trial with sevelamer hydrochloride, a greater number of peritonitis cases were reported in the sevelamer group than in the control group. Patients on peritoneal dialysis should be closely monitored to ensure the correct use of appropriate aseptic technique with the prompt recognition and management of any signs and symptoms associated with peritonitis.

Swallowing and choking difficulties

Difficulties swallowing the Sevelamer carbonate Winthrop tablet have been reported. Many of these cases involved patients with co-morbid conditions including swallowing disorders or oesophageal abnormalities. Proper swallowing ability should be carefully monitored in patients with co-morbid conditions. The use of sevelamer carbonate powder 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).

Hyperparathyroidism

Sevelamer carbonate is not indicated for the control of hyperparathyroidism. In patients with secondary hyperparathyroidism sevelamer carbonate 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 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 carbonate treatment should be re-evaluated in patients who develop severe gastrointestinal symptoms.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet that is to say essentially 'sodium-free'.

## 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 sevelamer carbonate, decreased the bioavailability of ciprofloxacin by approximately 50% when co-administered with sevelamer hydrochloride in a single dose study. Consequently, sevelamer carbonate 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 with 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. Therefore, possible reduction in absorption cannot be excluded. The anti-arrhythmic medical product should be taken at least one hour before or three hours after Sevelamer carbonate Winthrop, and blood monitoring can be considered.

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. Caution should be exercised when prescribing PPI to patients concomitantly treated with Sevelamer carbonate Winthrop. The phosphate serum level should be monitored and the sevelamer carbonate dosage adjusted consequently.

Bioavailability

Sevelamer carbonate 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 carbonate, or the physician should consider monitoring blood levels.

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.

## 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. Sevelamer carbonate 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 sevelamer carbonate should be made taking into account the benefit of breast-feeding to the child and the benefit of sevelamer carbonate 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 BSA.

## 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: nausea (very common), vomiting (very common), upper abdominal pain (very common), constipation (very common), diarrhea (common), dyspepsia (common) and flatulence (common).

Constipation can be an early symptom of serious gastrointestinal adverse reactions. The most serious adverse reactions are hypersensitivity (very rare frequency), intestinal obstruction (not known frequency), ileus/subileus (not known frequency), intestinal perforation (not known frequency), serious inflammatory gastrointestinal disorders associated with the presence of sevelamer crystals (not known frequency).

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 trials 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[1] Gastrointestinal 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] |

[1] See inflammatory gastrointestinal disorders warning in section 4.4

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 adverse reactions. In CKD patients, the maximum average daily dose studied was 14.4 grams of sevelamer carbonate in a single daily dose.

The symptoms observed in case of overdose are similar to adverse reactions listed in section 4.8, including mainly constipation and other known gastrointestinal disorders.

Appropriate symptomatic treatment should be provided.

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: All other therapeutic products, drugs for treatment of hyperkalemia and hyperphosphataemia. ATC code: V03A E02.

Mechanism of action

Sevelamer carbonate Winthrop contains sevelamer, a non-absorbed phosphate binding crosslinked polymer. 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.

Pharmacodynamic effects

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.

Clinical efficacy and safety

In two randomised, cross over clinical trials, 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 $1.5 \pm 0.3$ 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 $\geq 1.78$ mmol/L) haemodialysis patients over two randomised 4 week treatment periods (mean serum phosphorus time-weighted averages were $1.6 \pm 0.5$ mmol/L for sevelamer carbonate powder and $1.7 \pm 0.4$ mmol/L for sevelamer hydrochloride tablets).

In the clinical trials in haemodialysis patients, sevelamer alone did not have a consistent and clinically significant effect on 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 sevelamer carbonate 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 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.

Paediatric population

The safety and effectiveness of sevelamer carbonate in hyperphosphatemic paediatric patients with CKD was evaluated in a multicenter study with a 2-week, randomised, 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 randomised 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 BSA, in contrast however, no treatment response was observed in paediatric patients with qualifying phosphorus levels <7.0 mg/dL. Most of adverse reactions reported 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.

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.

## 5.3 Preclinical safety data

Non-clinical data 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 tumours 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 BSA).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Tablet core:

Microcrystalline cellulose
Sodium chloride
Zinc stearate

Film-coating:

Hypromellose (E464)
Diacetylated monoglycerides

### 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 child resistant polypropylene closure and a foil induction seal.
Each bottle contains 30 tablets or 180 tablets.
Packs of 1 bottle of 30 tablets or bottles of 180 tablets without outer carton.

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

Sanofi Winthrop Industrie
82 Avenue Raspail
94250 Gentilly
France

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/952/001 180 film-coated tablets
EU/1/14/952/004 30 film-coated tablets

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 January 2015
Date of latest renewal: 11 November 2019

## 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

Sevelamer carbonate Winthrop 0.8 g powder for oral suspension

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains 0.8 g sevelamer carbonate.

Excipient with known effect
This medicine contains 8.42 mg propylene glycol alginate (E405) in each 0.8 g sachet

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

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

Sevelamer carbonate Winthrop is also indicated for the control of hyperphosphataemia in adult patients with chronic kidney disease (CKD) not on dialysis with serum phosphorus ≥ 1.78 mmol/l.

Sevelamer carbonate Winthrop 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.

Sevelamer carbonate Winthrop 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. Sevelamer carbonate Winthrop 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, see section “Titration and maintenance”

*Children/adolescents (>6 years of age and a 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 BSA category. Sevelamer carbonate Winthrop 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, see section "Titration and maintenance"

For patients previously on phosphate binders (sevelamer hydrochloride or calcium based), Sevelamer carbonate Winthrop 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 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 dose based on 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 sevelamer carbonate should adhere to their prescribed diets.

Special populations

*Elderly population*
No dosage adjustment is necessary in the elderly population.

*Hepatic impairment*
No studies have been performed in patients with hepatic impairment.

*Paediatric population*
The safety and efficacy of Sevelamer carbonate Winthrop in children below the age of 6 years or in children with a BSA below 0.75 m$^2$ have not been established. No data are available.

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:

Oral use.

Each sachet of 0.8 g of powder is to be dispersed in 30 mL of water prior to administration (see section 6.6). The suspension should be ingested within 30 minutes after being prepared. Sevelamer carbonate Winthrop should be taken with food and not on an empty stomach.
As an alternative to water, the powder may be pre-mixed with a small amount of beverage or food (e.g. 100grams/120 ml) and consumed within 30 minutes. Sevelamer carbonate Winthrop powder should not be heated (e.g. microwave) or added to heated foods or liquids.

***(Instructions for presentation WITH dosing spoon)***
To achieve the correct dose, the dosing spoon provided in the carton must be used to measure 0.4 g of Sevelamer carbonate Winthrop. Further instructions are detailed in the patient leaflet.

***(Instructions for presentation WITHOUT dosing spoon)***

To achieve the correct dose when the sachet has to be divided, please use the dedicated presentation of 0.8 g powder with dosing spoon.

## 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 sevelamer carbonate have not been established in adult patients with chronic kidney disease not on dialysis with serum phosphorus < 1.78 mmol/l. Therefore it is currently not recommended for use in these patients.

The safety and efficacy of sevelamer carbonate 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

Treatment of these patients with Sevelamer carbonate Winthrop should only be initiated after careful benefit/risk assessment. If the therapy is initiated, patients suffering from these disorders should be monitored. Sevelamer carbonate treatment should be reevaluated in patients who develop severe constipation or other severe gastrointestinal symptoms.

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 sevelamer carbonate. The treatment should be re-evaluated in patients who develop severe constipation or other severe gastrointestinal symptoms.

Fat-soluble vitamins and folate deficiency

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 sevelamer carbonate 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 sevelamer carbonate. In patients undergoing peritoneal dialysis additional monitoring of fat-soluble vitamins and folic acid is recommended, since vitamin A, D, E and K levels were not measured in a clinical study in these patients.

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

Hypocalcaemia/hypercalcaemia

Patients with CKD may develop hypocalcaemia or hypercalcaemia. 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 CKD 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 trial with sevelamer hydrochloride, a greater number of peritonitis cases were reported in the sevelamer group than in the control group. Patients on peritoneal dialysis should be closely monitored to ensure the correct use of appropriate aseptic technique with the prompt recognition and management of any signs and symptoms associated with peritonitis.

Hypothyroidism

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

Hyperparathyroidism

Sevelamer carbonate is not indicated for the control of hyperparathyroidism. In patients with secondary hyperparathyroidism sevelamer carbonate 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 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 carbonate treatment should be re-evaluated in patients who develop severe gastrointestinal symptoms.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per sachet that is to say essentially ‘sodium-free’.

## 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 sevelamer carbonate, decreased the bioavailability of ciprofloxacin by approximately 50% when co-administered with sevelamer hydrochloride in a single dose study. Consequently, sevelamer carbonate 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 with 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. Therefore, possible reduction in absorption cannot be excluded. The anti-arrhythmic medicinal product should be taken at least one hour before or three hours after Sevelamer carbonate Winthrop and blood monitoring can be considered.

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. Caution should be exercised when prescribing PPI to patients concomitantly treated with Sevelamer carbonate Winthrop. The phosphate serum level should be monitored and the Sevelamer carbonate dosage adjusted consequently.

Bioavailability

Sevelamer carbonate 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 carbonate, or the physician should consider monitoring blood levels.

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.

## 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. Sevelamer carbonate 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 sevelamer carbonate should be made taking into account the benefit of breast-feeding to the child and the benefit of sevelamer carbonate 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 BSA.

## 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: nausea (very common), vomiting (very common), upper abdominal pain (very common), constipation (very common), diarrhea (common), dyspepsia (common) and flatulence (common).

Constipation can be an early symptom of serious gastrointestinal adverse reactions. The most serious adverse reactions are hypersensitivity (very rare frequency), intestinal obstruction (not known frequency), ileus/subileus (not known frequency), intestinal perforation (not known frequency), serious inflammatory gastrointestinal disorders associated with the presence of sevelamer crystals (not known frequency).

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 trials 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[1], Gastrointestinal 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] |

[1] See inflammatory gastrointestinal disorders warning in section 4.4

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 adverse reactions. In CKD patients, the maximum average daily dose studied was 14.4 grams of sevelamer carbonate in a single daily dose.

The symptoms observed in case of overdose are similar to adverse reactions listed in section 4.8, including mainly constipation and other known gastrointestinal disorders.

Appropriate symptomatic treatment should be provided.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: All other therapeutic products, drugs for treatment of hyperkalemia and hyperphosphataemia. ATC code: V03A E02.

Mechanism of action

Sevelamer carbonate Winthrop contains sevelamer, a non-absorbed phosphate binding crosslinked polymer. 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.

Pharmacodynamic effects

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.

Clinical efficacy and safety

In two randomised, cross over clinical trials, 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 $1.5 \pm 0.3$ 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 $\geq 1.78$ mmol/l) haemodialysis patients over two randomised 4 week treatment periods (mean serum phosphorus time-weighted averages were $1.6 \pm 0.5$ mmol/l for sevelamer carbonate powder and $1.7 \pm 0.4$ mmol/l for sevelamer hydrochloride tablets).

In the clinical trials in haemodialysis patients, sevelamer alone did not have a consistent and clinically significant effect on 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 carbonate 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 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.

Paediatric population

The safety and effectiveness of sevelamer carbonate in hyperphosphatemic paediatric patients with CKD was evaluated in a multicenter study with a 2-week, randomised, 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 randomised 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 BSA, in contrast however, no treatment response was observed in pediatric patients with qualifying phosphorus levels <7.0 mg/dL. Most of adverse reactions reported 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.

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.

## 5.3 Preclinical safety data

Non-clinical data 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 BSA).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Propylene glycol alginate (E405)
Citrus cream flavour
Sodium chloride
Sucralose
Iron oxide yellow (E172)

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years.

After reconstitution

The oral suspension must be administered within 30 minutes.

***(Instructions for presentation with dosing spoon)***
The sachet has to be discarded after 24 hours of opening

### 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

### 6.5 Nature and contents of container

Sachet of ethylene methacrylic acid copolymer, polyester, LDPE and aluminium foil laminate, with a heat seal.

Each sachet contains 0.8 g of sevelamer carbonate.

***(Instructions for presentation with dosing spoon)***
Each carton contains 90 sachets and a dosing spoon to measure the 0.4 g dose of powder.

### 6.6 Special precautions for disposal and other handling

The powder should be dispersed in 30 mL of water per sachet prior to administration. The suspension powder is pale yellow and has a citrus flavour.

The powder may also be pre-mixed with cold beverage or unheated food (see section 4.2). The powder should not be heated (e.g. microwave).

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

## 7. MARKETING AUTHORISATION HOLDER

Sanofi Winthrop Industrie
82 Avenue Raspail
94250 Gentilly
France

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/952/005 90 sachets
EU/1/14/952/006 90 sachets (with dosing spoon)

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 January 2015
Date of latest renewal: 11 November 2019

## 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

Sevelamer carbonate Winthrop 2.4 g powder for oral suspension

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains 2.4 g sevelamer carbonate.

Excipient with known effect
This medicine contains 25.27 mg propylene glycol alginate (E405) in each 2.4 g sachet.

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

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

Sevelamer carbonate Winthrop is also indicated for the control of hyperphosphataemia in adult patients with chronic kidney disease (CKD) not on dialysis with serum phosphorus $\geq$ 1.78 mmol/L.

Sevelamer carbonate Winthrop 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.

Sevelamer carbonate Winthrop 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. Sevelamer carbonate Winthrop 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, see section “Titration and maintenance”

*Children/adolescents (>6 years of age and a 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 BSA category. Sevelamer carbonate Winthrop 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, see section "Titration and maintenance"

For patients previously on phosphate binders (sevelamer hydrochloride or calcium based), Sevelamer carbonate Winthrop 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 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 dose based on 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 sevelamer carbonate should adhere to their prescribed diets.

Special populations

*Elderly population*
No dosage adjustment is necessary in the elderly population.

*Hepatic impairment*
No studies have been performed in patients with hepatic impairment.

*Paediatric population*
The safety and efficacy of Sevelamer carbonate Winthrop in children below the age of 6 years or in children with a BSA below 0.75 m$^2$ have not been established. No data are available.

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

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. Sevelamer carbonate Winthrop should be taken with food and not on an empty stomach.
As an alternative to water, the powder may be pre-mixed with a small amount of beverage or food (e.g. 100 grams/120 ml) and consumed within 30 minutes. Sevelamer carbonate Winthrop powder should not be heated (e.g. microwave) or added to heated foods or liquids.

If a dose of 0.4 g is to be administered, please use the dedicated 0.8 g powder presentation with dosing spoon.

## 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 sevelamer carbonate have not been established in adult patients with chronic kidney disease not on dialysis with serum phosphorus < 1.78 mmol/L. Therefore it is currently not recommended for use in these patients.

The safety and efficacy of sevelamer carbonate 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

Treatment of these patients with Sevelamer carbonate Winthrop should only be initiated after careful benefit/risk assessment. If the therapy is initiated, patients suffering from these disorders should be monitored. Sevelamer carbonate treatment should be reevaluated in patients who develop severe constipation or other severe gastrointestinal symptoms.

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 sevelamer carbonate. The treatment should be re-evaluated in patients who develop severe constipation or other severe gastrointestinal symptoms.

Fat-soluble vitamins and folate deficiency

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 sevelamer carbonate 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 sevelamer carbonate. In patients undergoing peritoneal dialysis additional

monitoring of fat-soluble vitamins and folic acid is recommended, since vitamin A, D, E and K levels were not measured in a clinical study in these patients.

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

Hypocalcaemia/hypercalcaemia

Patients with CKD may develop hypocalcaemia or hypercalcaemia. 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 CKD 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 clinicaltrial with sevelamer hydrochloride, a greater number of peritonitis cases were reported in the sevelamer group than in the control group. Patients on peritoneal dialysis should be closely monitored to ensure the correct use of appropriate aseptic technique with the prompt recognition and management of any signs and symptoms associated with peritonitis.

Hypothyroidism

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

Hyperparathyroidism

Sevelamer carbonate is not indicated for the control of hyperparathyroidism. In patients with secondary hyperparathyroidism sevelamer carbonate 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 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 carbonate treatment should be re-evaluated in patients who develop severe gastrointestinal symptoms.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per sachet that is to say essentially ‘sodium-free’.

## 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 sevelamer carbonate, decreased the bioavailability of ciprofloxacin by approximately 50% when co-administered with sevelamer hydrochloride in a single dose study. Consequently, sevelamer carbonate 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 with 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. Therefore, possible reduction in absorption cannot be excluded. The anti-arrhythmic medical product should be taken at least one hour before or three hours after Sevelamer carbonate Winthrop and blood monitoring can be considered.

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. Caution should be exercised when prescribing PPI to patients concomitantly treated with Sevelamer carbonate Winthrop. The phosphate serum level should be monitored and the sevelamer carbonate dosage adjusted consequently.

Bioavailability

Sevelamer carbonate 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 carbonate, or the physician should consider monitoring blood levels.

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.

## 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. Sevelamer carbonate 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 sevelamer carbonate should be made taking into account the benefit of breast-feeding to the child and the benefit of sevelamer carbonate 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 BSA.

## 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: nausea (very common), vomiting (very common), upper abdominal pain (very common), constipation (very common), diarrhea (common), dyspepsia (common) and flatulence (common).

Constipation can be an early symptom of serious gastrointestinal adverse reactions. The most serious adverse reactions are hypersensitivity (very rare frequency), intestinal obstruction (not known frequency), ileus/subileus (not known frequency), intestinal perforation (not known frequency), serious inflammatory gastrointestinal disorders associated with the presence of sevelamer crystals (not known frequency).

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 trials 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[1], Gastrointestinal 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] |

[1] See inflammatory gastrointestinal disorders warning in section 4.4

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 adverse reaction. In CKD patients, the maximum average daily dose studied was 14.4 grams of sevelamer carbonate in a single daily dose.

The symptoms observed in case of overdose are similar to adverse reactions listed in section 4.8, including mainly constipation and other known gastrointestinal disorders.

Appropriate symptomatic treatment should be provided.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: All other therapeutic products, drugs for treatment of hyperkalemia and hyperphosphataemia. ATC code: V03A E02.

Mechanism of action

Sevelamer carbonate Winthrop contains sevelamer, a non-absorbed phosphate binding crosslinked polymer. 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.

Pharmacodynamic effects

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.

Clinical efficacy and safety

In two randomised, cross over clinical trials, 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 $1.5 \pm 0.3$ 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 $\geq 1.78$ mmol/L) haemodialysis patients over two randomised 4 week treatment periods (mean serum phosphorus time-weighted averages were $1.6 \pm 0.5$ mmol/L for sevelamer carbonate powder and $1.7 \pm 0.4$ mmol/L for sevelamer hydrochloride tablets).

In the clinical trials in haemodialysis patients, sevelamer alone did not have a consistent and clinically significant effect on 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 sevelamer carbonate should be used within the context of a multiple therapeutic approach, which could include calcium as supplements, 1,25dihydroxy Vitamin $D_3$ or one of its analogues to lower the 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.

Paediatric population

The safety and effectiveness of sevelamer carbonate in hyperphosphatemic paediatric patients with CKD was evaluated in a multicenter study with a 2-week, randomised, 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 randomised 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 BSA, in contrast however, no treatment response was observed in paediatric patients with qualifying phosphorus levels <7.0 mg/dL. Most of adverse reactions reported 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.

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.

## 5.3 Preclinical safety data

Non-clinical data 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 tumours 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 BSA).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Propylene glycol alginate (E405)
Citrus Cream flavour
Sodium chloride
Sucralose
Iron oxide yellow (E172)

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years.

After reconstitution

The oral suspension must be administered within 30 minutes.
The sachet has to be discarded after 24 hours of opening.

### 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

### 6.5 Nature and contents of container

Sachet of ethylene methacrylic acid copolymer, polyester, LDPE 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.

The powder may also be pre-mixed with cold beverage or unheated food (see 4.2). The powder should not be heated (e.g. microwave).

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

## 7. MARKETING AUTHORISATION HOLDER

Sanofi Winthrop Industrie
82 Avenue Raspail
94250 Gentilly
France

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/952/002 60 sachets
EU/1/14/952/003 90 sachets

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 January 2015
Date of latest renewal: 11 November 2019

## 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 Ireland Limited
IDA Industrial Park
Old Kilmeaden Road
Waterford
IRELAND

Sanofi Winthrop Industrie
1 rue de la Vierge
Ambares et Lagrave
33565 Carbon Blanc cedex
France

ROVI Pharma Industrial Services, S.A.
Vía Complutense, 140, Alcalá de Henares,
Madrid, 28805, Spain

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 (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

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

- **Risk management plan (RMP)**

The marketing authorization holder (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.

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

# A. LABELLING

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**

**LABEL - BOTTLE OF 180 TABLETS WITHOUT OUTER CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

Sevelamer carbonate Winthrop 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 film-coated tablets

## 5. METHOD AND ROUTE OF ADMINISTRATION

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

Sanofi Winthrop Industrie
82 Avenue Raspail
94250 Gentilly
France

## 12. MARKETING AUTHORISATION NUMBERS

EU/1/14/952/001 180 film-coated tablets

## 13. BATCH NUMBER

Batch

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Sevelamer carbonate 800 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON – BOTTLE OF 30 TABLETS**

## 1. NAME OF THE MEDICINAL PRODUCT

Sevelamer carbonate Winthrop 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

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

Sanofi Winthrop Industrie
82 Avenue Raspail
94250 Gentilly
France

## 12. MARKETING AUTHORISATION NUMBERS

EU/1/14/952/004 30 film-coated tablets

## 13. BATCH NUMBER

Batch

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Sevelamer
carbonate
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**

## 1. NAME OF THE MEDICINAL PRODUCT

Sevelamer carbonate Winthrop 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

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

Sanofi Winthrop Industrie
82 Avenue Raspail
94250 Gentilly
France

## 12. MARKETING AUTHORISATION NUMBERS

EU/1/14/952/004 30 film-coated tablets

## 13. BATCH NUMBER

Batch

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

## 17. UNIQUE IDENTIFIER – 2D BARCODE

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

Sevelamer carbonate Winthrop 0.8 g powder for oral suspension
sevelamer carbonate

## 2. STATEMENT OF ACTIVE SUBSTANCE

Each sachet contains 0.8 g sevelamer carbonate.

## 3. LIST OF EXCIPIENTS

Contains propylene glycol (See leaflet for further information).

## 4. PHARMACEUTICAL FORM AND CONTENTS

Powder for oral suspension

90 sachets

## 5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
Oral 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

After reconstitution
The oral suspension must be administered within 30 minutes.

## 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

Sanofi Winthrop Industrie
82 Avenue Raspail
94250 Gentilly
France

## 12. MARKETING AUTHORISATION NUMBERS

EU/1/14/952/005 90 sachets
EU/1/14/952/006 90 sachets (with a dosing spoon)

## 13. BATCH NUMBER

Batch

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Sevelamer carbonate Winthrop
0.8 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

Sevelamer carbonate Winthrop 0.8 g powder for oral suspension
sevelamer carbonate

## 2. STATEMENT OF ACTIVE SUBSTANCE

Each sachet contains 0.8 g sevelamer carbonate.

## 3. LIST OF EXCIPIENTS

Contains propylene glycol (See leaflet for further information).

## 4. PHARMACEUTICAL FORM AND CONTENTS

Powder for oral suspension

0.8 g powder

## 5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
Oral 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

After reconstitution
The oral suspension must be administered within 30 minutes.

## 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

Sanofi Winthrop Industrie
82 Avenue Raspail
94250 Gentilly
France

## 12. MARKETING AUTHORISATION NUMBERS

EU/1/14/952/005 90 sachets
EU/1/14/952/006 90 sachets (with dosing spoon)

## 13. BATCH NUMBER

Batch

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

## 17. UNIQUE IDENTIFIER – 2D BARCODE

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON – CARTON OF 60 or 90 SACHETS**

## 1. NAME OF THE MEDICINAL PRODUCT

Sevelamer carbonate Winthrop 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

Contains propylene glycol (See leaflet for further information).

## 4. PHARMACEUTICAL FORM AND CONTENTS

Powder for oral suspension
60 sachets
90 sachets

## 5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
Oral 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

After reconstitution
The oral suspension must be administered within 30 minutes.

## 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

Sanofi Winthrop Industrie
82 Avenue Raspail
94250 Gentilly
France

## 12. MARKETING AUTHORISATION NUMBERS

EU/1/14/952/002 60 sachets
EU/1/14/952/003 90 sachets

## 13. BATCH NUMBER

Batch

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Sevelamer carbonate Winthrop
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

Sevelamer carbonate Winthrop 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

Contains propylene glycol (See leaflet for further information).

## 4. PHARMACEUTICAL FORM AND CONTENTS

Powder for oral suspension
2.4 g powder

## 5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
Oral 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

After reconstitution
The oral suspension must be administered within 30 minutes.

## 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

Sanofi Winthrop Industrie
82 Avenue Raspail
94250 Gentilly
France

## 12. MARKETING AUTHORISATION NUMBERS

EU/1/14/952/002 60 sachets
EU/1/14/952/003 90 sachets

## 13. BATCH NUMBER

Batch

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

## 17. UNIQUE IDENTIFIER – 2D BARCODE

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

# B. PACKAGE LEAFLET

**Package leaflet: Information for the user**

**Sevelamer carbonate Winthrop 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 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 Sevelamer carbonate Winthrop is and what it is used for

Sevelamer carbonate Winthrop contains the active substance sevelamer carbonate. It binds phosphate from food in the digestive tract and so reduces serum phosphorus levels in the blood.

This medicine 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.

This medicine 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 Sevelamer carbonate Winthrop

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

**Warnings and precautions**
Talk to your doctor before taking Sevelamer carbonate Winthrop:
- if you have swallowing problems. Your doctor can rather prescribe sevelamer carbonate powder for oral suspension.
- if you have problems with motility (movement) in your stomach and bowel
- if you have active inflammation of the bowel

- if you have undergone major surgery on your stomach or bowel.

Talk to your doctor while taking Sevelamer carbonate Winthrop:
- if you experience severe abdominal pain, stomach or intestine disorders, or blood in the stool (gastrointestinal bleeding). These symptoms can be due to serious inflammatory bowel disease caused by sevelamer crystal deposit in your bowel. Contact your doctor who will decide on continuing the treatment or not.

*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 this medicine 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.
- have disturbed level of bicarbonate in your blood and increased acidity in the blood and other body tissue. Your doctor should monitor the level of bicarbonate in your blood.

*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.

**Children**
Do not give this medicine to children below the age of 6 years because the safety and efficacy in children (below the age of 6 years) have not been studied.

**Other medicines and Sevelamer carbonate Winthrop**
Tell your doctor if you are taking, have recently taken or might take any other medicines.

- Sevelamer carbonate Winthrop 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 Sevelamer carbonate Winthrop.

- The effects of medicines such as ciclosporin, mycophenolate mofetil and tacrolimus (medicines used to suppress the immune system) may be reduced by Sevelamer carbonate Winthrop. 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 Sevelamer carbonate Winthrop. Therefore your doctor may monitor the levels of thyroid stimulating hormone in your blood more closely.

- Medicines treating heartburn and reflux from your stomach or oesophagus, such as omeprazole, pantoprazole, or lansoprazole, known as “proton pump inhibitors”, may reduce the efficacy of Sevelamer carbonate Winthrop. Your doctor may monitor the phosphate level in your blood.

Your doctor will check for interactions between Sevelamer carbonate Winthrop and other medicines on a regular basis.

In some cases where Sevelamer carbonate Winthrop 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 Sevelamer carbonate Winthrop intake. Your doctor may also consider monitoring the levels of that medicine in your blood.

**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.
The potential risk of Sevelamer carbonate Winthrop during human pregnancy is unknown. Talk to your doctor who will decide if you can continue the treatment with Sevelamer carbonate Winthrop.

It is unknown whether Sevelamer carbonate Winthrop is excreted in breast milk and may affect your baby. Talk to your doctor who will decide if you can breastfeed your baby or not, and if it is necessary to stop Sevelamer carbonate Winthrop treatment.

**Driving and using machines**
Sevelamer carbonate Winthrop is unlikely to affect your ability to drive or to use machines.

**Excipients**
This medicine contains less than 1 mmol sodium (23 mg) per tablet that is to say essentially 'sodium-free'.

## 3. How to take Sevelamer carbonate Winthrop

Always take this medicine exactly as your doctor has told you. He will base the dose on your serum phosphorus level.

The recommended starting dose of this medicine for adults and elderly is one to two tablets of 800 mg with each meal, 3 times a day. Check with your doctor, pharmacist or nurse if you are not sure.

Take Sevelamer carbonate Winthrop after your meal or with food.

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 Sevelamer carbonate Winthrop when necessary to reach an adequate phosphate level.

Follow the diet prescribed by your doctor.

**If you take more Sevelamer carbonate Winthrop than you should**
In the event of a possible overdose you should contact your doctor immediately.

**If you forget to take Sevelamer carbonate Winthrop**
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.

**If you stop taking Sevelamer carbonate Winthrop**
Taking your Sevelamer carbonate Winthrop treatment is important to maintain an appropriate phosphate level in your blood. Stopping Sevelamer carbonate Winthrop would lead to important consequences such as calcification in the blood vessels. If you consider stopping your Sevelamer carbonate Winthrop treatment, contact your doctor or pharmacist first.
If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

## 4. Possible side effects

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

Constipation is a very common side effect. It can be an early symptom of a blockage in your intestine. In case of constipation, please inform your doctor or pharmacist if you experience it.

Some side effects could be serious. If you get any of the following side effects, seek immediate medical attention:
- Allergic reaction (signs including rash, hives, swelling, trouble breathing). This is a very rare side effect (may affect up to 1 in 10,000 people).
- Blockage in the intestine (signs include: severe bloating; abdominal pain, swelling or cramps; severe constipation) has been reported. Frequency is not known.
- Rupture in the intestinal wall (signs include: severe stomach pain, chills, fever, nausea, vomiting, or a tender abdomen) has been reported. Frequency is not known.
- Serious inflammation of the large bowel (symptoms include: severe abdominal pain, stomach or intestine disorders, or blood in the stool [gastrointestinal bleeding]) and crystal deposit in the intestine have been reported. Frequency is not known.

Other side effects have been reported in patients taking Sevelamer carbonate Winthrop:

**Very common** (may affect more than 1 in 10 people):
- vomiting,
- upper abdominal pain,
- nausea.

**Common** (may affect up to 1 in 10 people):
- diarrhoea,
- stomach ache,
- indigestion,
- flatulence.

**Not known** (frequency cannot be estimated from the available data):
- cases of itching,
- rash,
- slow intestine motility (movement).

**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 Sevelamer carbonate Winthrop

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/or carton after "EXP". The expiry date refers to the last day of that month.

Keep the bottle container tightly closed in order to protect from moisture.
This medicine does not require any special temperature 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 Sevelamer carbonate Winthrop contains**

- The active substance is sevelamer carbonate. Each film-coated tablet contains 800 mg of sevelamer carbonate.

- The other ingredients are microcrystalline cellulose, sodium chloride, zinc stearate, hypromellose (E464), diacetylated monoglycerides.

**What Sevelamer carbonate Winthrop looks like and contents of the pack**

Sevelamer carbonate Winthrop film-coated tablets are white to off-white oval tablets with RV800 engraved on one side. The tablets are packed in high density polyethylene bottles with a child-resistant polypropylene closure and an induction seal.

Pack sizes:
Each bottle contains 30 tablets or 180 tablets.
Packs of 1 bottle of 30 tablets or 180 tablets with no outer carton
Not all pack sizes may be marketed.

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

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**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.

**Package leaflet: Information for the user**

**Sevelamer carbonate Winthrop 0.8 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 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 Sevelamer carbonate Winthrop is and what it is used for

Sevelamer carbonate Winthrop contains the active substance sevelamer carbonate. It binds phosphate from food in the digestive tract and so reduces serum phosphorus levels in the blood.

This medicine 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).

This medicine 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 Sevelamer carbonate Winthrop

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

**Warnings and precautions**
Talk to you doctor before taking Sevelamer carbonate Winthrop:
- if you have problems with motility (movement) in your stomach and bowel
- if you have active inflammation of the bowel

- if you have undergone major surgery on your stomach or bowel.

Talk to your doctor while taking Sevelamer carbonate Winthrop:
- if you experience severe abdominal pain, stomach or intestine disorders, or blood in the stool (gastrointestinal bleeding). These symptoms can be due to serious inflammatory bowel disease caused by sevelamer crystal deposit in your bowel. Contact your doctor who will decide on continuing the treatment or not.

*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 this medicine 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.
- have disturbed level of bicarbonate in your blood and increased acidity in the blood and other body tissue. Your doctor should monitor the level of bicarbonate in your blood.

*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.

**Children**
Do not give this medicine to children below the age of 6 years because the safety and efficacy in children (below the age of 6 years) have not been studied.

**Other medicines and Sevelamer carbonate Winthrop**
Tell your doctor if you are taking or have recently taken or might take any other medicines.

- Sevelamer carbonate Winthrop 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 Sevelamer carbonate Winthrop.

- The effects of medicines such as ciclosporin, mycophenolate mofetil and tacrolimus (medicines used to suppress the immune system) may be reduced by Sevelamer carbonate Winthrop. 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 Sevelamer carbonate Winthrop. Therefore your doctor may monitor the levels of thyroid stimulating hormone in your blood more closely.

- Medicines treating heartburn and reflux from your stomach or oesophagus, such as omeprazole, pantoprazole, or lansoprazole, known as “proton pump inhibitors”, may reduce the efficacy of Sevelamer carbonate Winthrop. Your doctor may monitor the phosphate level in your blood.

Your doctor will check for interactions between Sevelamer carbonate Winthrop and other medicines on a regular basis.

In some cases where Sevelamer carbonate Winthrop 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 Sevelamer carbonate Winthrop intake. Your doctor may also consider monitoring the levels of that medicine in your blood.

**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. The potential risk of Sevelamer carbonate Winthrop during human pregnancy is unknown. Talk to your doctor who will decide if you can continue the treatment with Sevelamer carbonate Winthrop.

It is unknown whether Sevelamer carbonate Winthrop is excreted in breast milk and may affect your baby. Talk to your doctor who will decide if you can breastfeed your baby or not, and if it is necessary to stop Sevelamer carbonate Winthrop treatment.

**Driving and using machines**
Sevelamer carbonate Winthrop is unlikely to affect your ability to drive or to use machines.

**Excipients**
This medicine contains less than 1 mmol sodium (23 mg) per sachet that is to say essentially 'sodium-free'.

This medicine contains 8.42 mg propylene glycol in each 0.8 g sachet.

## 3. How to take Sevelamer carbonate Winthrop

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

For a 0.8 g dose, the powder for oral suspension should be dispersed in 30 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.
Instead of water, the powder may be pre-mixed with a small amount of cold beverage (about 120 ml or half a glass) or food (about 100 grams) and consumed within 30 minutes. Do not heat Sevelamer carbonate Winthrop powder (e.g. microwave) or add to hot foods or liquids.

The recommended starting dose of this medicine for adults and elderly is 2.4-4.8g per day equally divided over three meals. Check with your doctor, pharmacist or nurse if you are not sure. The exact starting dose and regimen will be determined by your doctor.

Take Sevelamer carbonate Winthrop after your meal or with food.

***(Instructions for presentation with dosing spoon)***
For 0.4 g doses, the powder in the sachet may be divided. In this case the 0.4 g dose of Sevelamer Carbonate Winthrop powder must be measured using the dosing spoon provided in the carton.

Always use the dosing spoon provided in the carton.

***(Instructions for presentation WITHOUT dosing spoon)***
If a dose of 0.4 g is to be administered, please use the dedicated 0.8 g powder presentation with dosing spoon.

**Use in children and adolescents**
The recommended starting dose of Sevelamer carbonate Winthrop for children is based on their height and weight (used to calculate body surface area by your physician). For children, the powder is preferred, as tablets are not appropriate in this population. This medicine 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 0.8 g, the powder in the sachet may be divided. The 0.4 g dose of Sevelamer carbonate Winthrop powder must be measured using the dosing spoon provided in the carton.

*Preparation using a dosing spoon:*

Use the provided dosing spoon for each 0.4 g dose of Sevelamer Carbonate Winthrop powder.

For a 0.4 g dose:

- Shake the sachet holding the top corner before opening, to move the powder to the bottom of the sachet
- Open the sachet by tearing along the marked line.
- Ensure the dosing spoon is dry.
- Hold the dosing spoon horizontally and pour the powder out of the sachet into the dosing spoon.
- Fill the powder to the spoon level.
- Do not tap the dosing spoon to compact the powder.
- Mix the powder from the dosing spoon in 30 mL of water. Stir the suspension and drink it within 30 minutes of being prepared. It is important to drink all of the liquid to ensure that all of the powder is swallowed.
- Close the sachet by folding over twice.
- The remaining powder may be used within 24 hours for the next dose.
- Discard sachets of powder that have been opened for more than 24 hours.

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

Follow the diet prescribed by your doctor.

**If you take more Sevelamer carbonate Winthrop than you should**
In the event of a possible overdose you should contact your doctor immediately.

**If you forget to take Sevelamer carbonate Winthrop**
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.

**If you stop taking Sevelamer carbonate Winthrop**
Taking your Sevelamer carbonate Winthrop treatment is important to maintain an appropriate phosphate level in your blood. Stopping Sevelamer carbonate Winthrop would lead to important consequences such as calcification in the blood vessels. If you consider stopping your Sevelamer carbonate Winthrop treatment, contact your doctor or pharmacist first.
If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

## 4. Possible side effects

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

Constipation is a very common side effect. It can be an early symptom of a blockage in your intestine.In case of constipation, please inform your doctor or pharmacist if you experience it.

Some side effects could be serious. If you get any of the following side effects, seek immediate medical attention:
- Allergic reaction (signs including rash, hives, swelling, trouble breathing). This is a very rare side effect (may affect up to 1 in 10,000 people).
- Blockage in the intestine (signs include: severe bloating; abdominal pain, swelling or cramps; severe constipation) has been reported. Frequency is not known.
- Rupture in the intestinal wall (signs include: severe stomach pain, chills, fever, nausea, vomiting, or a tender abdomen) has been reported. Frequency is not known.

- Serious inflammation of the large bowel (symptoms include: severe abdominal pain, stomach or intestine disorders, or blood in the stool [gastrointestinal bleeding]) and crystal deposit in the intestine have been reported. Frequency is not known.

Other side effects have been reported in patients taking Sevelamer carbonate Winthrop:

Very common (may affect more than 1 in 10 people):
- vomiting,
- upper abdominal pain,
- nausea.

Common (may affect up to 1 in 10 people):
- diarrhoea,
- stomach ache,
- indigestion,
- flatulence.

Not known (frequency cannot be estimated from the available data):
- cases of itching,
- rash,
- slow intestine motility (movement).

**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 Sevelamer carbonate Winthrop

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 expiry date refers to the last day of that month.

The reconstituted suspension must be administered within 30 minutes of reconstitution.
This medicine does not require any special storage conditions.

***(Instructions for presentation with dosing spoon)***
Discard the sachet after 24 hours of opening.

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 Sevelamer carbonate Winthrop contains**

- The active substance is sevelamer carbonate. Each sachet contains 0.8 g of sevelamer carbonate.
- The other ingredients are propylene glycol alginate (E405), citrus cream flavour, sodium chloride, sucralose and iron oxide yellow (E172).

**What Sevelamer carbonate Winthrop looks like and contents of the pack**

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

***(Instructions for presentation with dosing spoon)***
A 0,4 g dosing spoon is provided in the carton.

Pack size:
90 sachets per carton

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**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.

**Package leaflet: Information for the user**

**Sevelamer carbonate Winthrop 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 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 Sevelamer carbonate Winthrop is and what it is used for

Sevelamer carbonate Winthrop contains the active substance sevelamer carbonate. It binds phosphate from food in the digestive tract and so reduces serum phosphorus levels in the blood.

This medicine 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).

This medicine 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 Sevelamer carbonate Winthrop

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

**Warnings and Precautions**

Talk to your doctor before taking Sevelamer carbonate Winthrop :
- if you have problems with motility (movement) in your stomach and bowel

- if you have active inflammation of the bowel
- if you have undergone major surgery on your stomach or bowel.

Talk to your doctor while taking Sevelamer carbonate Winthrop:
- if you experience severe abdominal pain, stomach or intestine disorders, or blood in the stool (gastrointestinal bleeding). These symptoms can be due to serious inflammatory bowel disease caused by sevelamer crystal deposit in your bowel. Contact your doctor who will decide on continuing the treatment or not.

*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 this medicine 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.
- have disturbed level of bicarbonate in your blood and increased acidity in the blood and other body tissue. Your doctor should monitor the level of bicarbonate in your blood.

*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.

**Children**
Do not give this medicine to children below the age of 6 years because because the safety and efficacy in children (below the age of 6 years) have not been studied.

**Other medicines and Sevelamer carbonate Winthrop**
Tell your doctor if you are taking or have recently taken or might take any other medicines.

- Sevelamer carbonate Winthrop 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 Sevelamer carbonate Winthrop.

- The effects of medicines such as ciclosporin, mycophenolate mofetil and tacrolimus (medicines used to suppress the immune system) may be reduced by Sevelamer carbonate Winthrop. 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 Sevelamer carbonate Winthrop. Therefore your doctor may monitor the levels of thyroid stimulating hormone in your blood more closely.

- Medicines treating heartburn and reflux from your stomach or oesophagus, such as omeprazole, pantoprazole, or lansoprazole, known as “proton pump inhibitors”, may reduce the efficacy of Sevelamer carbonate Winthrop. Your doctor may monitor the phosphate level in your blood.

Your doctor will check for interactions between Sevelamer carbonate Winthrop and other medicines on a regular basis.

In some cases where Sevelamer carbonate Winthrop 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 Sevelamer carbonate Winthrop intake. Your doctor may also consider monitoring the levels of that medicine in your blood.

**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. The potential risk of Sevelamer carbonate Winthrop during human pregnancy is unknown. Talk to your doctor who will decide if you can continue the treatment with Sevelamer carbonate Winthrop.

It is unknown whether Sevelamer carbonate Winthrop is excreted in breast milk and may affect your baby. Talk to your doctor who will decide if you can breastfeed your baby or not, and if it is necessary to stop Sevelamer carbonate Winthrop treatment.

**Driving and using machines**
Sevelamer carbonate Winthrop is unlikely to affect your ability to drive or to use machines.

**Excipients**
This medicine contains less than 1 mmol sodium (23 mg) per sachet that is to say essentially 'sodium-free'.

This medicine contains 25.27 mg propylene glycol in each 2.4 g sachet.

## 3. How to take Sevelamer carbonate Winthrop

Always take this medicine exactly as your doctor has told you. He 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.
Instead of water, the powder may be pre-mixed with a small amount of cold beverage (about 120 ml or half a glass) or food (about 100 grams) and consumed within 30 minutes. Do not heat Sevelamer carbonate Winthrop powder (e.g. microwave) or add to hot foods or liquids.

The recommended starting dose of this medicine for adults and elderly is 2.4-4.8g per day equally divided over three meals. The exact starting dose and regimen will be determined by your doctor. Check with your doctor, pharmacist or nurse if you are not sure.

Take Sevelamer carbonate Winthrop after your meal or with food.

If a dose of 0.4 g is to be administered, please use the dedicated 0.8 g powder presentation with dosing spoon.

**Use in children and adolescents**
The recommended starting dose of Sevelamer carbonate Winthrop for children is based on their height and weight (used to calculate body surface area by your physician). For children, the powder is preferred, as tablets are not appropriate for this population. This medicine 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.

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

Follow the diet prescribed by your doctor.

**If you take more Sevelamer carbonate Winthrop than you should**
In the event of a possible overdose you should contact your doctor immediately.

**If you forget to take Sevelamer carbonate Winthrop**
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.

**If you stop taking Sevelamer carbonate Winthrop**
Taking your Sevelamer carbonate Winthrop treatment is important to maintain an appropriate phosphate level in your blood. Stopping Sevelamer carbonate Winthrop would lead to important consequences such as calcification in the blood vessels. If you consider stopping your Sevelamer carbonate Winthrop treatment, contact your doctor or pharmacist first.
If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

## 4. Possible side effects

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

Constipation is a very common side effect. It can be an early symptom of a blockage in your intestine.In case of constipation, please inform your doctor or pharmacist if you experience it.

Some side effects could be serious. If you get any of the following side effects, seek immediate medical attention:
- Allergic reaction (signs including rash, hives, swelling, trouble breathing). This is a very rare side effect (may affect up to 1 in 10,000 people).
- Blockage in the intestine (signs include: severe bloating; abdominal pain, swelling or cramps; severe constipation) has been reported. Frequency is not known.
- Rupture in the intestinal wall (signs include: severe stomach pain, chills, fever, nausea, vomiting, or a tender abdomen) has been reported. Frequency is not known.
- Serious inflammation of the large bowel (symptoms include: severe abdominal pain, stomach or intestine disorders, or blood in the stool [gastrointestinal bleeding]) and crystal deposit in the intestine have been reported. Frequency is not known.

Other side effects have been reported in patients taking Sevelamer carbonate Winthrop:

Very common (may affect more than 1 in 10 people):
- vomiting,
- upper abdominal pain,
- nausea.

Common (may affect up to 1 in 10 people):
- diarrhoea,
- stomach ache,
- indigestion,
- flatulence.

Not known (frequency cannot be estimated from the available data):
- cases of itching,
- rash,
- slow intestine motility (movement).

**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 Sevelamer carbonate Winthrop

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 "EXP". The expiry date refers to the last day of that month.

The reconstituted suspension must be administered within 30 minutes of reconstitution.
This medicine 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 Sevelamer carbonate Winthrop contains**

- The active substance is sevelamer carbonate. Each sachet contains 2.4 g of sevelamer carbonate.
- The other ingredients are propylene glycol alginate (E405), citrus cream flavour, sodium chloride, sucralose and iron oxide yellow (E172).

**What Sevelamer carbonate Winthrop looks like and contents of the pack**

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

Pack size:
60 sachets per carton
90 sachets per carton

Not all pack sizes may be marketed.

**Marketing Authorisation Holder**

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

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**Other sources of information**

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