Space for Edge code

Package Leaflet

ERSISA-S

Sevelamer Carbonate for Oral Suspension, 2.4 g

amneal®

==========

1. NAME OF THE MEDICINAL PRODUCT

ERSISA-S (Sevelamer Carbonate for Oral Suspension, 2.4 g)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition:
Each packet contains 2.4 grams of sevelamer carbonate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for oral suspension.

White to off-white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ERSISA-S is indicated for the control of serum phosphorus in adults and children 6 years of age and older with chronic kidney disease (CKD) on dialysis.

4.2 Posology and method of administration

General Dosing Information

Starting Dose for Adult Patients Not Taking a Phosphate Binder
The recommended starting dose of sevelamer carbonate for oral suspension is 0.8 to 1.6 g taken orally with meals based on serum phosphorus level. Table 1 provides recommended starting doses of sevelamer carbonate for oral suspension for adult patients not taking a phosphate binder.

Table 1: Starting Dose for Adult Dialysis Patients Not Taking a Phosphate Binder

Serum Phosphorus	*Sevelamer Carbonate for Oral Suspension*
> 5.5 and < 7.5 mg/dL	0.8 g three times daily with meals
≥ 7.5 mg/dL	1.6 g three times daily with meals

Dose Titration for Adult Patients Taking Sevelamer Carbonate for Oral Suspension
Titrate the sevelamer carbonate for oral suspension dose by 0.8 g three times per day with meals at two-week intervals as necessary to achieve target serum phosphorus levels. Based on clinical studies, the average prescribed adult daily dose of sevelamer carbonate is approximately 7.2 g per day. The highest daily adult dose of sevelamer carbonate studied was 14 grams in CKD patients on dialysis.

Starting Dose for Pediatric Patients Not Taking a Phosphate Binder
The recommended starting dose for pediatric patients 6 years of age and older is 0.8 g to 1.6 g taken three times per day with meals based on the patient's body surface area (BSA) category; see Table 2.

Table 2: Recommended Starting Dosage and Titration Increment Based on Pediatric Patient's Body Surface Area (m^2)

BSA (m^2)	*Starting Dose Per Meal/Snack*	*Titration Increases/ Decreases Per Dose*
≥ 0.75 to < 1.2	0.8 g	Titrate by 0.4 g
≥ 1.2	1.6 g	Titrate by 0.8 g

Dose Titration for Pediatric Patients Taking Sevelamer Carbonate for Oral Suspension
Titrate the sevelamer carbonate for oral suspension dose as needed to achieve target levels at two-week intervals based on BSA category, as shown in Table 2.

Switching from Sevelamer Hydrochloride Tablets
For adult patients switching from sevelamer hydrochloride tablets to sevelamer carbonate powder, use the same dose in grams.

Switching between Sevelamer Carbonate Tablets and Powder
Use the same dose in grams.

Switching from Calcium Acetate
Table 3 gives recommended starting doses of sevelamer carbonate for oral suspension based on a patient's current calcium acetate dose.

Table 3: Starting Dose for Dialysis Patients Switching from Calcium Acetate to Sevelamer Carbonate for Oral Suspension

Calcium Acetate 667 mg (Tablets per meal)	*Sevelamer Carbonate for Oral Suspension*
1 tablet	0.8 g
2 tablets	1.6 g
3 tablets	2.4 g

4.3 Contraindications

Sevelamer carbonate for oral suspension is contraindicated in patients with bowel obstruction.

Sevelamer carbonate for oral suspension is contraindicated in patients with known hypersensitivity to sevelamer carbonate, sevelamer hydrochloride, or to any of the excipients.

4.4 Special warnings and precautions for use

Gastrointestinal Adverse Events

Patients with dysphagia, swallowing disorders, severe gastrointestinal (GI) motility disorders, including severe constipation, or major GI tract surgery were not included in the sevelamer carbonate clinical studies.

Cases of dysphagia and esophageal tablet retention have been reported in association with use of the tablet formulation of sevelamer, some requiring hospitalization and intervention. Consider using sevelamer suspension in patients with a history of swallowing disorders.

Cases of bowel obstruction, bleeding gastrointestinal ulcers, colitis, ulceration, necrosis, and perforation have also been reported with sevelamer use (see section 4.8). Inflammatory disorders may resolve upon sevelamer carbonate discontinuation. Treatment with sevelamer carbonate should be re-evaluated in patients who develop severe gastrointestinal symptoms.

Reductions in Vitamins D, E, K (clotting factors) and Folic Acid Levels

In preclinical studies in rats and dogs, sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, reduced vitamins D, E, and K (coagulation parameters) and folic acid levels at doses of 6 to 10 times the recommended human dose. In short-term clinical trials, there was no evidence of reduction in serum levels of vitamins. However, in a one-year clinical trial, 25-hydroxyvitamin D (normal range 10 to 55 ng/mL) fell from 39 ± 22 ng/mL to 34 ± 22 ng/mL ($p<0.01$) with sevelamer hydrochloride treatment. Most (approximately 75%) patients in sevelamer hydrochloride clinical trials were receiving vitamin supplements.

4.5 Interaction with other medicinal products and other forms of interaction

There are no empirical data on avoiding drug interactions between sevelamer carbonate and most concomitant oral drugs. For oral medication where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy (e.g., cyclosporine, tacrolimus, levothyroxine), consider separation of the timing of the administration of the two drugs (see section 5.2). The duration of separation depends upon the absorption characteristics of the medication concomitantly administered, such as the time to reach peak systemic levels and whether the drug is an immediate-release or an extended-release product. Where possible consider monitoring clinical responses and/or blood levels of concomitant drugs that have a narrow therapeutic range.

Table 4: Sevelamer Drug Interactions

Oral drugs for which sevelamer did not alter the pharmacokinetics when administered concomitantly
Digoxin
Enalapril
Iron
Metoprolol
Warfarin

Oral drugs that have demonstrated interaction with sevelamer and are to be dosed separately from sevelamer carbonate	
	Dosing Recommendations
Ciprofloxacin	Take at least 2 hours before or 6 hours after sevelamer
Mycophenolate mofetil	Take at least 2 hours before sevelamer

4.6 Fertility, pregnancy and lactation

Pregnancy

Risk Summary
Sevelamer carbonate is not absorbed systemically following oral administration and maternal use is not expected to result in fetal exposure to the drug.

Clinical Considerations
Sevelamer carbonate may decrease serum levels of fat soluble vitamins and folic acid in pregnant women (see section 5.2). Consider supplementation.

Data

Animal data

In pregnant rats given dietary doses of 0.5, 1.5 or 4.5 g/kg/day of sevelamer hydrochloride during organogenesis, reduced or irregular ossification of fetal bones, probably due to a reduced absorption of fat-soluble vitamin D, occurred in mid and high-dose groups (human equivalent doses approximately equal to 3 to 4 times the maximum clinical trial dose of 13 g). In pregnant rabbits given oral doses of 100, 500 or 1,000 mg/kg/day 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).

Lactation

Risk Summary
Sevelamer carbonate is not absorbed systemically by the mother following oral administration, and breastfeeding is not expected to result in exposure of the child to sevelamer carbonate.

Clinical Considerations
Sevelamer carbonate may decrease serum levels of fat soluble vitamins and folic acid in pregnant women (see section 5.2). Consider supplementation.

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

4.8.1 Adverse reactions

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

There are limited clinical trial data on the safety of sevelamer carbonate. However, because it contains the same active ingredient as the hydrochloride salt, the adverse event profiles of the two salts are expected to be similar. In a cross-over study in hemodialysis patients with treatment durations of eight weeks each and no washout, and another cross-over study in hemodialysis patients with treatment durations of four weeks each and no washout between treatment periods, the adverse reactions on sevelamer carbonate powder were similar to those reported for sevelamer hydrochloride.

In a parallel design study of sevelamer hydrochloride with treatment duration of 52 weeks, adverse reactions reported for sevelamer hydrochloride (n=99) were similar to those reported for the active-comparator group (n=101). Overall adverse reactions among those treated with sevelamer hydrochloride occurring in > 5% of patients included: vomiting (22%), nausea (20%), diarrhea (19%), dyspepsia (16%), abdominal pain (9%), flatulence (8%), and constipation (8%). A total of 27 patients treated with sevelamer and 10 patients treated with comparator withdrew from the study due to adverse reactions.

Based on studies of 8 to 52 weeks, the most common reason for withdrawal from sevelamer hydrochloride was gastrointestinal adverse reactions (3% to 16%).

In 143 peritoneal dialysis patients studied for 12 weeks using sevelamer hydrochloride, most common adverse reactions were similar to adverse reactions observed in hemodialysis patients. The most frequently occurring treatment emergent serious adverse reaction was peritonitis (8 reactions in 8 patients [8%] in the sevelamer group and 2 reactions in 2 patients [4%] on active-control). Thirteen patients (14%) in the sevelamer group and 9 patients (20%) in the active-control group discontinued, mostly for gastrointestinal adverse reactions.

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or to establish a causal relationship to drug exposure.

The following adverse reactions have been identified during use of sevelamer hydrochloride or sevelamer carbonate: hypersensitivity, pruritus, rash, abdominal pain, bleeding gastrointestinal ulcers, colitis, ulceration, necrosis, fecal impaction, and uncommon cases of ileus, intestinal obstruction, and intestinal perforation. Appropriate medical management should be given to patients who develop constipation or have worsening of existing constipation to avoid severe complications.

4.8.2 Clinical Studies Experience (upon request from any regulatory Authority in GCC)

4.8.3 Post-marketing Experience (upon request from any regulatory Authority in GCC)

To reports any side effect(s):

Saudi Arabia:

- The National Pharmacovigilance Centre (NPC):
  - SFDA Call Center: 19999
  - E-mail: npc.drug@sfda.gov.sa
  - Website: https://ade.sfda.gov.sa/

4.9 Overdose

In CKD patients on dialysis, the maximum dose studied was 14 grams of sevelamer carbonate and 13 grams of sevelamer hydrochloride. There are no reports of overdosage with sevelamer carbonate or sevelamer hydrochloride in patients. Since sevelamer is not absorbed, the risk of systemic toxicity is low.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of Action

Sevelamer carbonate for oral suspension contains sevelamer carbonate, a non-absorbed phosphate-binding cross-linked polymer, free of metal and calcium. It contains multiple amines separated by one carbon from the polymer backbone. These amines exist in a protonated form in the intestine and interact with phosphate molecules through ionic and hydrogen bonding. By binding phosphate in the gastrointestinal tract and decreasing absorption, sevelamer carbonate lowers the phosphate concentration in the serum (serum phosphorus).

Pharmacodynamics

In addition to effects on serum phosphorus levels, sevelamer hydrochloride has been shown to bind bile acids *in vitro* and *in vivo* in experimental animal models. Because sevelamer binds bile acids, it may interfere with normal fat absorption and thus may reduce absorption of fat soluble vitamins such as A, D and K. In clinical trials of sevelamer hydrochloride, both the mean total and LDL cholesterol declined by 15% to 31%; the clinical significance of this finding, which was observed after 2 weeks, is unclear. Triglycerides, HDL cholesterol, and albumin did not change.

5.2 Pharmacokinetic properties

A mass balance study using ^{14}C-sevelamer hydrochloride, in 16 healthy male and female volunteers showed that sevelamer hydrochloride is not systemically absorbed. No absorption studies have been performed in patients with renal disease.

Drug Interactions

In vivo

Sevelamer carbonate has been studied in human drug-drug interaction studies (9.6 grams once daily with a meal) with warfarin and digoxin. Sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, has been studied in human drug-drug interaction studies (2.4 to 2.8 grams single-dose or three times daily with meals or two times daily without meals) with ciprofloxacin, digoxin, enalapril, iron, metoprolol, mycophenolate mofetil, and warfarin.

Co-administered single-dose of 2.8 grams of sevelamer hydrochloride in fasted state decreased the bioavailability of ciprofloxacin by approximately 50% in healthy subjects. Concomitant administration of sevelamer and mycophenolate mofetil in adult and pediatric patients decreased the mean MPA C_{max} and $AUC_{0\text{-}12h}$ by 36% and 26% respectively. Sevelamer carbonate or sevelamer hydrochloride did not alter the pharmacokinetics of enalapril, digoxin, iron, metoprolol, and warfarin when co-administered.

Cases of increased thyroid stimulating hormone (TSH) levels have been reported in patients co-administered sevelamer hydrochloride and levothyroxine. Reduction in concentrations of cyclosporine and tacrolimus leading to dose increases has also been reported in transplant patients when co-administered with sevelamer hydrochloride without any clinical consequences (for example, graft rejection). The possibility of an interaction cannot be excluded with these drugs.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

Standard lifetime carcinogenicity bioassays were conducted in mice and rats. Rats were given sevelamer hydrochloride by diet at 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 13 g). Mice received dietary administration of sevelamer hydrochloride at doses of up to 9 g/kg/day (human equivalent dose 3 times the maximum clinical trial dose). There was no increased incidence of tumors observed in mice.

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.

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 3 times the maximum clinical trial dose of 13 g).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose, NF (Avicel PH-102)
Propylene Glycol Alginate, NF (Protanal® Ester K3B426)
Sodium Chloride, USP (EMPROVE®exp)
Sucralose, NF (Splenda®)
FT- 4174 NIA Lemon FLVP Flavor
Silicon Dioxide, NF (SYLOID®244FP)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 Years

After reconstitution

The oral suspension must be administered within 30 minutes.

6.4 Special precautions for storage

Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from moisture. Keep out of the sight and reach of children.

6.5 Nature and contents of container

ERSISA-S is supplied as opaque, foil lined, heat sealed, packets containing 2.4 g of sevelamer carbonate on an anhydrous basis. 90 packets are packed in a carton.

6.6 Special precautions for disposal <and other handling>

Sevelamer carbonate powder is available in 2.4 g packets. Place the sevelamer carbonate powder in a cup and suspend in the amount of water described in Table 5.

Table 5: Sevelamer Carbonate Powder Preparation Instructions

Amount of Sevelamer Carbonate Powder	*Minimum Amount of Water for Dose Preparation (either ounces, mL, or tablespoon)*		
	Ounces	*mL*	*Tablespoons*
0.4 g	1	30	2
0.8 g	1	30	2
2.4 g	2	60	4

Instruct patients to stir the mixture vigorously (it does not dissolve), resuspend, if necessary, right before administration, and drink the entire preparation within 30 minutes.

As an alternative to water, the entire contents of the packet may be pre-mixed with a small amount of food or beverage and consumed immediately (within 30 minutes) as part of the meal. Do not heat sevelamer carbonate powder (e.g., microwave) or add to heated foods or liquids.

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

7. MARKETING AUTHORISATION HOLDER

Impax Laboratories, LLC

8. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

9. DATE OF REVISION OF THE TEXT

Iss. 08-2023-00

10. DOSIMETRY

Not Applicable

11. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not Applicable