HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SEVELAMER CARBONATE safely and effectively. See full prescribing information for SEVELAMER CARBONATE.

SEVELAMER CARBONATE tablets, for oral use
SEVELAMER CARBONATE powder, for oral suspension
Initial U.S. Approval: 2000

RECENT MAJOR CHANGES

INDICATIONS AND USAGE
• Sevelamer carbonate is a phosphate binder indicated for the control of serum phosphorus in adults and children 6 years of age and older with chronic kidney disease on dialysis. (1)

DOSAGE AND ADMINISTRATION
• Starting dose of sevelamer carbonate is 0.8 or 1.6 grams administered orally three times per day with meals based on serum phosphorus levels for adult patients and based on body surface area (BSA) category for pediatric patients. (2.1)
• Titrate by 0.8 g per meal in two-week intervals for adult patients as needed to obtain serum phosphorus target. (2.1)
• Titrate based on BSA category for pediatric patients in two-week intervals for 6 weeks and then every 4 weeks as needed to obtain serum phosphorus target. (2.1)

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

<table>
<thead>
<tr>
<th>Serum Phosphorus</th>
<th>Sevelamer Carbonate</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;5.5 and ≤7.5 mg/dL</td>
<td>0.8 g three times daily with meals</td>
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<tr>
<td>≥7.5 mg/dL</td>
<td>1.6 g three times daily with meals</td>
</tr>
</tbody>
</table>

Table 2: Recommended Starting Dosage and Titration Increment Based on Pediatric Patient’s Body Surface Area (m²)

<table>
<thead>
<tr>
<th>BSA (m²)</th>
<th>Starting Dose Per Meal/ Snack</th>
<th>Titration Increases/Decreases Per Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥0.75 to &lt;1.2</td>
<td>0.8 g</td>
<td>Titrate by 0.4 g</td>
</tr>
<tr>
<td>≥1.2</td>
<td>1.6 g</td>
<td>Titrate by 0.8 g</td>
</tr>
</tbody>
</table>

Dose Titration for Adult Patients Taking Sevelamer Carbonate. Titrate the sevelamer carbonate 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 tablets or 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 based on a patient’s current calcium acetate dose.

1 INDICATIONS AND USAGE
Sevelamer carbonate 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.

2 DOSAGE AND ADMINISTRATION
2.1 General Dosing Information
Starting Dose for Adult Patients Not Taking a Phosphate Binder. The recommended starting dose of sevelamer carbonate 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 adult patients not taking a phosphate binder.

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

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Dose Titration for Adult Patients Taking Sevelamer Carbonate. Titrate the sevelamer carbonate 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 g in CKD patients on dialysis.

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CONTRAINDICATIONS
• Bowel obstruction. (4)
• Known hypersensitivity to sevelamer carbonate, sevelamer hydrochloride, or to any of the excipients. (4)

WARNINGS AND PRECAUTIONS
• Serious cases of dysphagia, bowel obstruction, bleeding gastrointestinal ulcers, colitis, ulceration, necrosis, and perforation have been associated with sevelamer use, some requiring hospitalization and surgery. (5.1)

ADVERSE REACTIONS
• Most of the safety experience is with sevelamer carbonate tablets and sevelamer hydrochloride. In long-term studies with sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, the most common adverse events included: vomiting (22%), nausea (20%), diarrhea (19%), dyspepsia (16%), abdominal pain (9%), flatulence (8%), and constipation (8%). (5.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genzyme Corporation at 1-800-847-0069 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS
• For oral medication where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy, consider separation of the timing of administration and/or monitor clinical responses or blood levels of the concomitant medication. (7)
• Sevelamer did not alter the pharmacokinetics of digoxin, enalapril, iron, metoprolol and warfarin. (7)
• Sevelamer has demonstrated interaction with ciprofloxacin, mycophenolate mofetil, and therefore, these drugs should be dosed separately from sevelamer carbonate. (7)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 04/2020
The following adverse reactions have been identified during postapproval use of sevelamer hydrochloride or sevelamer carbonate: hypersensitivity, pruritus, rash, abdominal pain, bleeding gastrointestinal ulcers, colitis, ulceration, necrosis, fecal impaction, and uncommon cases of fever, intestinal obstruction, and intestinal perforation. Appropriate medical management should be given to patients who develop constriction or have worsening of existing constriction to avoid severe complications.

### 7 DRUG INTERACTIONS

There are no formal drug-drug interaction studies 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 Clinical Pharmacology (12.5)]. 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.

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 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 Clinical Pharmacology (12.2)]. 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 3–4 times the maximum clinical trial dose of 13 g). In pregnant rabbits given oral doses of 100, 500, or 1000 mg/kg/day of sevelamer hydrochloride by gavage during organogenesis, an increase in early resorptions occurred in the high-dose group (human equivalent dose twice the maximum clinical trial dose).

#### 8.2 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 Clinical Pharmacology (12.2)]. Consider supplementation.

#### 8.4 Pediatric Use

The safety and efficacy of sevelamer carbonate in lowering serum phosphorus levels was studied in patients 6 years of age and older with CKD. In this study, sevelamer carbonate was apparently less effective in children with a low baseline serum phosphorus, which described children <13 years of age and children not on dialysis. Given its mechanism of action, sevelamer carbonate is expected to be effective in lowering serum phosphorus levels in pediatric patients with CKD. Most adverse events that were reported as related, or possibly related, to sevelamer carbonate were gastrointestinal in nature. No new risks or safety signals were identified with the use of sevelamer carbonate in the trial.

Sevelamer carbonate has not been studied in pediatric patients below 6 years of age.

#### 8.5 Geriatric Use

Clinical studies of sevelamer carbonate did not include sufficient numbers of subjects aged 65 and over to determination whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range.

#### 10 OVERDOSAGE

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.

#### 11 DESCRIPTION

The active ingredient is sevelamer carbonate, a polymeric amine that binds phosphate and is meant for oral administration. It was developed as a pharmaceutical alternative to sevelamer hydrochloride.

Sevelamer carbonate is an anion exchange resin, with the same polymeric structure as sevelamer hydrochloride, in which calcium replaces chloride as the counterion. While the counterions differ for the two salts, the polymer itself, the active moiety involved in phosphate binding, is the same.

Sevelamer carbonate is known chemically as poly(allylamine-co-N,N'-diallyl-1,3-diamino-2-hydroxypropane) carbonate salt. Sevelamer carbonate is hygroscopic, but insoluble in water.
14 CLINICAL STUDIES

The ability of sevelamer to control serum phosphorus in CKD patients on dialysis was predominantly determined from the effects of the hydrochloride salt to bind phosphate. Six clinical trials used sevelamer hydrochloride and three clinical trials used sevelamer carbonate. The sevelamer hydrochloride studies include one double-blind, placebo-controlled 2-week study (sevelamer N=24); two open-label, uncontrolled, 8-week studies (sevelamer N=220); and three active-controlled open-label studies with treatment durations of 8 to 52 weeks (sevelamer N=256). The sevelamer carbonate studies include one double-blind, active-controlled, cross-over study with two 8-week treatment periods using sevelamer carbonate tablets (N=79); one open-label, active-controlled, cross-over study with two 4-week treatment periods using sevelamer carbonate powder (N=31); and one randomized, parallel, open-label study using sevelamer carbonate powder (N=144) dosed once daily or sevelamer hydrochloride tablets (N=73) dosed three times daily for 24 weeks. Six of the active-controlled studies are described here (three sevelamer carbonate and three sevelamer hydrochloride studies).

14.1 Cross-Over Study of Sevelamer Carbonate 800 mg Tablets and Sevelamer Hydrochloride 800 mg Tablets

Stage 5 CKD patients on hemodialysis were entered into a five-week sevelamer hydrochloride run-in period and then patients were randomized to receive, in a parallel-group design, sevelamer carbonate 800 mg tablets or sevelamer hydrochloride 800 mg tablets for eight weeks each, with no intervening washout. Study dose during the cross-over period was determined based on the sevelamer hydrochloride dose during the run-in period on a gram-per-gram basis. The phosphorus levels at the end of each of the two cross-over periods were similar. Average actual daily dose was 6.0 g/day divided among meals for both treatments. Thirty-nine of those completing the cross-over portion of the study were entered into a two-week washout period during which patients were instructed not to take any phosphate binders; this confirmed the activity of sevelamer in this study.

14.2 Cross-Over Study of Sevelamer Carbonate Powder and Sevelamer Hydrochloride Tablets

Stage 5 CKD patients on hemodialysis were entered into a four-week sevelamer hydrochloride run-in period and then patients received, in random order, sevelamer carbonate powder and sevelamer hydrochloride tablets for four weeks each with no intervening washout. Study dose during the cross-over period was determined based on the sevelamer hydrochloride dose during the run-in period on a gram-per-gram basis. The phosphorus levels at the end of each of the two cross-over periods were similar. Average actual daily dose was 6.0 g/day divided among meals for sevelamer carbonate powder and 6.4 g/day divided among meals for sevelamer hydrochloride tablets.

14.3 Clinical Study of Sevelamer Carbonate Powder and Tablets in Pediatric Patients

A clinical study with sevelamer carbonate was conducted in 101 patients 6 to 18 years of age with chronic kidney disease. This study included a washout period for patients on a phosphate binder, a 2-week, double-blind, fixed-dose period (FDP) in which patients were randomized to sevelamer carbonate (n=50) or placebo (n=51), and a 26-week, open-label, sevelamer carbonate dose titration period (DTP). Most patients were 13 to 18 years of age (73%) and had a BSA ≥1.2 m² (84%). Approximately 78% of patients were CKD patients on dialysis. Sevelamer carbonate significantly reduced serum phosphorus during Week 2 (primary endpoint) by an LS Mean difference of -0.79 (SE 0.27 mg/dL) compared to placebo (p=0.001). A similar treatment response was observed in patients who received sevelamer carbonate during the 6-month open-label DTP. Approximately 30% of subjects reached their target serum phosphorus. The median prescribed daily dose was approximately 7.0 g per day during the titration period. The results of the primary efficacy endpoint were consistent by BSA subgroup. In contrast, a treatment response was not observed in subjects with a baseline serum phosphorus below 7 mg/dL, many of whom were the subjects 6 to <13 years of age or the subjects not on dialysis (Figure 2).

Figure 2: Change in Serum Phosphorus (mg/dL) from Baseline to Week 2 by Subgroup

[a]: LS Mean difference of Sevelamer Carbonate – Placebo, based on ANCOVA within subgroup with treatment as fixed effect and screening BSA and baseline serum phosphorus as covariates.

14.4 Sevelamer Hydrochloride versus Active-Control, Cross-Over Study in Hemodialysis Patients

Eighty-four CKD patients on hemodialysis who were hyperphosphatemic (serum phosphorus >6.0 mg/dL) following a two-week phosphate binder washout period were randomized in a cross-over design to receive in random order sevelamer hydrochloride and active control for eight weeks each. Treatment periods were separated by a two-week phosphate binder washout period. Patients started on treatment three times per day with meals. Over each eight-week treatment period, at three separate time points the dose of sevelamer hydrochloride could be titrated up to control serum phosphorus, the dose of active control could also be altered to attain phosphorus control. Both treatments significantly decreased mean serum phosphorus by about 2 mg/dL (Table 6).

[Caption]: LS Mean difference of Sevelamer Carbonate – Placebo, based on ANCOVA within subgroup with treatment as fixed effect and screening BSA and baseline serum phosphorus as covariates.
Two hundred CKD patients on hemodialysis who were hyperphosphatemic (serum phosphorus >5.5 mg/dL) following a two-week phosphate binder washout period were randomized to receive sevelamer hydrochloride (N=99) or active control (N=101). At week 52, using last observation carried forward, sevelamer and active control both significantly decreased mean serum phosphorus hydrochloride 800 mg tablets (N=99) or an active control (N=101). At week 52, using last observation carried forward, sevelamer hydrochloride and active control. The median response is a reduction of about 2 mg/dL in both groups. The distribution of responses is shown in Figure 3. The distributions are similar for sevelamer hydrochloride and active control. About 50% of subjects have reductions between 1 and 3 mg/dL. Sixty-one percent of sevelamer hydrochloride patients and 73% of the control patients completed the study.

Average daily sevelamer hydrochloride dose at the end of treatment was 4.9 g (range of 0.0 to 12.6 g).

### 14.5 Sevelamer Hydrochloride versus Active Control in Hemodialysis Patients

Two hundred CKD patients on hemodialysis who were hyperphosphatemic (serum phosphorus >5.5 mg/dL) following a two-week phosphate binder washout period were randomized to receive sevelamer hydrochloride 800 mg tablets (N=99) or an active control (N=101). At week 52, using last observation carried forward, sevelamer and active control both significantly decreased mean serum phosphorus (Table 7).

### Table 7: Mean Serum Phosphorus (mg/dL) at Baseline and Endpoint

<table>
<thead>
<tr>
<th></th>
<th>Sevelamer Hydrochloride (N=99)</th>
<th>Active Control (N=99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>8.4</td>
<td>8.0</td>
</tr>
<tr>
<td>Endpoint</td>
<td>6.4</td>
<td>5.9</td>
</tr>
<tr>
<td>Change from Baseline at Endpoint (95% Confidence Interval)</td>
<td>-2.0 (-2.5, -1.5)</td>
<td>-2.1 (-2.6, -1.7)</td>
</tr>
</tbody>
</table>

*p<0.0001, within treatment group comparison

The distribution of responses is shown in Figure 3. The distributions are similar for sevelamer hydrochloride and active control. About 50% of subjects have reductions between 1 and 3 mg/dL.

### 14.6 Sevelamer Hydrochloride versus Active Control in Peritoneal Dialysis Patients

One hundred and forty-three patients on peritoneal dialysis who were hyperphosphatemic (serum phosphorus >5.5 mg/dL) following a two-week phosphate binder washout period were randomized to receive sevelamer hydrochloride (N=97) or active control (N=46) open label for 12 weeks. Average daily sevelamer hydrochloride dose at the end of treatment was 5.9 g (range 0.8 to 14.3 g). Thirteen patients (14%) in the sevelamer group and 9 patients (20%) in the active-control group discontinued, mostly for gastrointestinal adverse reactions. There were statistically significant changes in serum phosphorus (p<0.001) for sevelamer hydrochloride (1.8 mg/dL from baseline of 7.5 mg/dL) similar to the active control.

### 14.7 Once-Daily versus Three-Times-Per-Day Dosing

Stage 5 CKD patients on hemodialysis with a serum phosphate level of >5.5 mg/dL after washout from baseline therapies were randomized in a 2:1 ratio to receive either sevelamer carbonate powder once daily (N=144) or sevelamer hydrochloride as a tablet with the dose divided three times per day (N=73) for 24 weeks. The initial dose for the two groups was 4.8 g/day. At the end of the study, the total daily dose was 6.2 g/day of sevelamer carbonate powder once daily and 6.7 g/day of sevelamer hydrochloride tablets three times per day. A greater percentage of subjects on the once-daily dose than threetimes-per-day regimen discontinued therapy prematurely, 35% versus 15%. The reasons for discontinuation were largely driven by adverse events and withdrawal of consent in the once-daily dosing regimen. Serum phosphate levels and calcium-phosphate product were better controlled on the threetimes-per-day regimen than on the once-daily regimen. Mean serum phosphorus decreased 2.0 mg/dL for sevelamer carbonate powder once daily and 2.9 mg/dL for sevelamer hydrochloride tablets three times per day.

### 16 HOW SUPPLIED/STORAGE AND HANDLING

Tablets: Sevelamer carbonate tablets for oral use is supplied as white oval, film-coated, compressed tablets, imprinted with RENVELA 800, containing 800 mg of sevelamer carbonate on an anhydrous basis.

- 1 Bottle of 270 ct 800 mg tablets (NDC 0955-1050-27)
- powdered

Powder: Sevelamer carbonate for oral suspension is supplied as opaque, foil-lined, heat-sealed, packets containing 0.8 g or 2.4 g of sevelamer carbonate on an anhydrous basis.

- 1 Box (NDC 0955-1054-90) of 90 ct 2.4 g packets (NDC 0955-1054-01)
- 1 Box (NDC 0955-1052-90) of 90 ct 0.8 g packets (NDC 0955-1052-01)


[See USP controlled room temperature]

Protect from moisture.

### 17 PATIENT COUNSELING INFORMATION

Inform patients to take sevelamer carbonate with meals and adhere to their prescribed diets.

For patients using an oral medication where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy, advise the patient to take the oral medication at least one hour before or three hours after sevelamer carbonate.

For sevelamer carbonate powder, brief the patient on preparation of the powder in water.

Advise patients to report new onset or worsening of existing constipation or bloody stools promptly to their physician [see Warnings and Precautions (5.1)].

Manufactured for:
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Bridgewater, NJ 08807
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SEVC-G-FPLR-SL-APR20 Rx Only

Average daily sevelamer hydrochloride dose at the end of treatment was 6.5 g (range of 0.8 to 13 g).