INDICATIONS AND USAGE

Renvela® (sevelamer carbonate) is indicated for the control of serum phosphorus in adults and children 6 years of age and older with chronic kidney disease on dialysis. (1)

**Starting Dose for Adult Patients Not Taking a Phosphate Binder.**

The recommended starting dose of Renvela 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)

**DOSAGE FORMS AND STRENGTHS**

- Tablets: 800 mg (3)
- Powder: 0.8 g and 2.4 g packets (3)

**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%). (6.1)

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 Renvela. (7)

See 17 for PATIENT COUNSELING INFORMATION

**FULL PRESCRIBING INFORMATION: CONTENTS**

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
  2.1 General Dosing Information
  2.2 Sevelamer Carbonate Powder Preparation Instructions
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
  5.1 Gastrointestinal Adverse Events
  5.2 Reductions in Vitamins D, E, K (clotting factors) and Folic Acid Levels
6 ADVERSE REACTIONS
  6.1 Clinical Trials Experience
  6.2 Postmarketing Experience
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
  8.1 Pregnancy
  8.2 Lactation
  8.4 Pediatric Use
  8.5 Geriatric Use
9 SAFETY INFORMATION
10 OVERDOSE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
  12.1 Mechanism of Action
  12.2 Pharmacodynamics
  12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
  13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
  14.1 Cross-Over Study of Sevelamer Carbonate (Renvela) 800 mg Tablets and Sevelamer Hydrochloride (Renagel) 800 mg Tablets
  14.2 Cross-Over Study of Sevelamer Carbonate (Renvela) Powder and Sevelamer Hydrochloride (Renagel) Tablets
  14.3 Clinical Study of Sevelamer Carbonate (Renvela) Powder and Tablets in Pediatric Patients
  14.4 Sevelamer Hydrochloride versus Active-Control, Cross-Over Study in Hemodialysis Patients
  14.5 Sevelamer Hydrochloride versus Active Control in Hemodialysis Patients
  14.6 Sevelamer Hydrochloride versus Active Control in Peritoneal Dialysis Patients
  14.7 Once-Daily versus Three-Times-Per-Day Dosing
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed*
hydroxyvitamin D (normal range 10 to 55 ng/mL) fell from 39 ± 22 ng/mL to 34 ± 22 ng/mL (p = 0.01). Reductions in vitamins D, E, K (clotting factors) and folic acid levels were observed.

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

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.

6.1 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.

6.2 Postmarketing Experience

Based on the adverse reactions 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 postapproval use of sevelamer hydrochloride or sevelamer carbonate: hypersensitivity, pruritus, rash, abdominal pain, bloating 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 complications or have worsening of existing constipation to avoid severe complications.

7. DRUG INTERACTIONS

There are no empirical data on avoiding drug interactions between Renvela 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 (12.3)]. 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 Carbonate Powder Preparation Instructions

<table>
<thead>
<tr>
<th>Amount of Renvela Powder</th>
<th>Minimum Amount of Water for Dose Preparation (either ounces, mL, or tablespoon)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.4 g</td>
<td>1 ounce 30 mL 2 tablespoons</td>
</tr>
<tr>
<td>0.8 g</td>
<td>1 ounce 30 mL 2 tablespoons</td>
</tr>
<tr>
<td>2.4 g</td>
<td>2 ounces 60 mL 4 tablespoons</td>
</tr>
</tbody>
</table>

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 package 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 Renvela powder (e.g., microwave) or add to heated foods or liquids.

3. DOSAGE FORMS AND STRENGTHS

Tablets: 800 mg white oval, film-coated, compressed tablets, engraved with RV800 on one side. Powder: 0.8 g and 2.4 g pale-yellow powder packaged in an opaque, foil-lined, heat-sealed packets.

4. CONTRAINDICATIONS

Renvela is contraindicated in patients with bowel obstruction. Renvela is contraindicated in patients with known hypersensitivity to sevelamer carbonate, sevelamer hydrochloride, or to any of the excipients.

5. WARNINGS AND PRECAUTIONS

5.1 Gastrointestinal Adverse Events

Patients with diabetic nephropathy, renal insufficiency, severe gastrointestinal (GI) motility disorders, severe constipation, or major GI tract surgery were not included in the Renvela 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 Adverse Reactions (6.2)]. Inflammatory disorders may resolve upon Renvela discontinuation. Treatment with Renvela should be re-evaluated in patients who develop severe gastrointestinal symptoms.

5.2 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 6–10 times the recommended human dose. In short-term clinical trials, there was no evidence of lowering of 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.

6. ADVERSE REACTIONS

6.1 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 Renvela. 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, severe gastrointestinal adverse events 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 of early resorptions occurred in the high-dose group (human equivalent dose twice the maximum clinical trial dose).

6.2 Lactation

Risk Summary: Renvela is not absorbed systemically by the mother following oral administration, and breastfeeding is not expected to result in exposure of the child to Renvela. 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 vitamins 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 of early resorptions occurred in the high-dose group (human equivalent dose twice the maximum clinical trial dose).

6.3 Pediatric Use

Risk Summary: Renvela is contraindicated in patients with known hypersensitivity to sevelamer carbonate, sevelamer hydrochloride, or to any of the excipients. 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 vitamins 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 of early resorptions occurred in the high-dose group (human equivalent dose twice the maximum clinical trial dose).

6.3 Pediatric Use

Risk Summary: Renvela is not absorbed systemically by the mother following oral administration, and breastfeeding is not expected to result in exposure of the child to Renvela. 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 vitamins 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 of early resorptions occurred in the high-dose group (human equivalent dose twice the maximum clinical trial dose).

6.3 Pediatric Use

Risk Summary: Renvela is contraindicated in patients with known hypersensitivity to sevelamer carbonate, sevelamer hydrochloride, or to any of the excipients.
Concomitant administration of sevelamer and mycophenolate mofetil in adult and pediatric patients decreased the mean MPA C bioavailability of ciprofloxacin by approximately 50% in healthy subjects. A single dose or three times daily with meals or two times daily without meals) with ciprofloxacin, digoxin, and warfarin and digoxin. Sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate has been studied in human drug-drug interaction studies (9.6 grams once daily on an anhydrous basis. The inactive ingredients are natural and artificial citrus flavor, propylene glycol alginate, sodium chloride, sucrose, and ferric oxide (yellow).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Renvela Powder: Each packet of Renvela powder contains 0.8 or 2.4 g of sevelamer carbonate on an anhydrous basis. The inactive ingredients are hypromellose, diacetylated monoglycerides, microcrystalline cellulose, sodium chloride, and zinc stearate.

Renvela Tablets: Each film-coated tablet of Renvela contains 800 mg of sevelamer carbonate on an anhydrous basis. The inactive ingredients are hypromellose, diacetylated monoglycerides, microcrystalline cellulose, sodium chloride, and ferric oxide (yellow).

12.2 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%–31%; the clinical significance of this finding, which was observed after 2 weeks, is unclear. Triglycerides, HDL cholesterol, and albumin did not change.

12.3 Pharmacokinetics

A mass balance study using 14C-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 (2.4–2.8 g of sevelamer single dose or three times daily with meals or two times daily without meals) with ciprofloxacin, digoxin, enalapril, iron, metoprolol, mycophenolate mofetil, and warfarin. Coadministered single dose of 2.8 grams of sevelamer hydrochloride in fasted state decreased the bioavailability of ciprofloxacin by approximately 53% in healthy subjects. Concomitant administration of sevelamer and mycophenolate mofetil in adult and pediatric patients decreased the mean MPA cmax and AUC0–12h by 36% and 26%, respectively. Sevelamer carbonate or sevelamer hydrochloride did not alter the pharmacokinetics of enalapril, digoxin, iron, metoprolol, and warfarin when coadministered.

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

13 NONCLINICAL TOXICOLOGY

13.1 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 metabolite 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).

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. Three 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 2–8 week treatment periods using sevelamer carbonate tablets (N=79); one open-label, active-controlled, cross-over study with 2–4 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).
The distribution of responses is shown in Figure 3. The distributions are similar for sevelamer hydrochloride and active control. The median response is a reduction of about 2 mg/dL in both groups. About 50% of subjects have reductions between 1 and 3 mg/dL.

Figure 3: Percentage of Patients (Y-axis) Attaining a Phosphorus Reduction from Baseline (mg/dL) at Least as Great as the Value of the X-axis

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) and Ion Product at Baseline and Change from Baseline to End of Treatment

<table>
<thead>
<tr>
<th></th>
<th>Sevelamer HCl (N=94)</th>
<th>Active Control (N=98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphorus Baseline</td>
<td>7.5</td>
<td>7.3</td>
</tr>
<tr>
<td>Change from Baseline</td>
<td>-2.1</td>
<td>-1.8</td>
</tr>
<tr>
<td>Ca × Phosphorus Ion Product Baseline</td>
<td>70.5</td>
<td>68.4</td>
</tr>
<tr>
<td>Change from Baseline</td>
<td>-19.4</td>
<td>-14.2</td>
</tr>
</tbody>
</table>

Sixty-one percent of sevelamer hydrochloride patients and 73% of the control patients completed the full 52 weeks of treatment.

Figure 4, a plot of the phosphorus change from baseline for the completers, illustrates the durability of response for patients who are able to remain on treatment.

Figure 4: Mean Phosphorus Change from Baseline for Patients who Completed 52 Weeks of Treatment

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

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 800 mg tablets (N=99) or an active control (N=101). Average daily sevelamer hydrochloride dose at the end of treatment was 6.5 g (range 0.8 to 13 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 (>1.6 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 three-times-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 three-times-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.