

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Renvela safely and effectively. See full prescribing information for Renvela.

Renvela (sevelamer carbonate) Tablet, Film Coated for Oral use
Renvela (sevelamer carbonate) For Oral Suspension
Initial U.S. Approval: 2000

RECENT MAJOR CHANGES

- Dosage and Administration (2) (08/2009)

INDICATIONS AND USAGE

- Renvela® is a phosphate binder indicated for the control of serum phosphorus in patients with chronic kidney disease on dialysis. (1)

DOSAGE AND ADMINISTRATION

- Starting dose of Renvela is 0.8 or 1.6 grams administered orally three times per day with meals. (2.1)
- Titrate by 0.8 g per meal in two week intervals as needed to obtain serum phosphorus target (3.5 to 5.5 mg/dL). (2.1)
- Switch gram-for-gram among sevelamer formulations. Further titration may be necessary to achieve desired phosphorus levels. (2.1)

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

- Bowel obstruction. (4)

WARNINGS AND PRECAUTIONS

- Serious cases of dysphagia, bowel obstruction, 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 tablets. The most frequently occurring adverse reactions in a short term study with sevelamer carbonate tablets (8-week cross-over) study were: nausea (3%) and vomiting (3%). In a short term study of sevelamer carbonate powder, adverse events were similar to those reported for sevelamer carbonate tablets. 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)
- Cases of fecal impaction and, less commonly, ileus, bowel obstruction and bowel perforation have been reported. (6.2)

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

- Sevelamer decreases the bioavailability of ciprofloxacin by approximately 50%. (7.1)
- Sevelamer did not alter the pharmacokinetics of single doses of digoxin, warfarin, enalapril, metoprolol, or iron. (7)
- When administering an oral medication where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy, administer the drug at least one hour before or three hours after Renvela, and monitor blood levels of the drug. (7.7)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 05/2011

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*Sections or subsections omitted from the full prescribing information are not listed

1 **FULL PRESCRIBING INFORMATION**2 **1 INDICATIONS AND USAGE**

3 Renvela® (sevelamer carbonate) is indicated for the control of serum phosphorus in
4 patients with chronic kidney disease (CKD) on dialysis.

5 **2 DOSAGE AND ADMINISTRATION**

6 Because of the rapid reaction with the hydrochloric acid in the stomach, the dosing of
7 Renvela powder or tablet is anticipated to be similar to that of the sevelamer
8 hydrochloride salt or tablet.

9 **2.1 General Dosing Information**

10 Renvela should be given three times a day with meals.

11 *Patients Not Taking a Phosphate Binder.* The recommended starting dose of Renvela is
12 0.8 to 1.6 g with meals based on serum phosphorus level. [Table 1](#) provides
13 recommended starting doses of Renvela for patients not taking a phosphate binder.

14 **Table 1. Starting Dose for Dialysis Patients Not Taking a Phosphate Binder**

Serum Phosphorus	Renvela® 800 mg Tablet	Renvela Powder
> 5.5 and < 7.5 mg/dL	1 tablet three times daily with meals	0.8 g three times daily with meals
≥ 7.5 mg/dL	2 tablets three times daily with meals	1.6 g three times daily with meals

15
16 *Switching from Sevelamer Hydrochloride Tablets.* For patients switching from sevelamer
17 hydrochloride tablets to sevelamer carbonate tablets or powder, use the same dose in
18 grams. Further titration may be necessary to achieve desired phosphorus levels. The
19 highest daily dose of sevelamer carbonate studied was 14 grams in CKD patients on
20 dialysis.

21 *Switching between Sevelamer Carbonate Tablets and Powder.* Use the same dose in
22 grams. Further titration may be necessary to achieve desired phosphorus levels.

23 *Switching from Calcium Acetate.* In a study in 84 CKD patients on hemodialysis, a
24 similar reduction in serum phosphorus was seen with equivalent doses (approximately
25 mg for mg) of sevelamer hydrochloride and calcium acetate. [Table 2](#) gives recommended
26 starting doses of Renvela based on a patient's current calcium acetate dose.

27 **Table 2. Starting Dose for Dialysis Patients Switching From**
 28 **Calcium Acetate to Renvela**

Calcium Acetate 667 mg (Tablets per meal)	Renvela® 800 mg Tablet (Tablets per meal)	Renvela Powder
1 tablet	1 tablet	0.8 g
2 tablets	2 tablets	1.6 g
3 tablets	3 tablets	2.4 g

29 *Dose Titration for All Patients Taking Renvela.* Titrate the Renvela dose by 0.8 g three
 30 times per day with meals at two-week intervals as necessary with the goal of controlling
 31 serum phosphorus within the target range.

32 **2.2 Sevelamer Carbonate Powder Preparation Instructions**

33 The entire contents of each 0.8 or 2.4 g packet should be placed in a cup and mixed
 34 thoroughly with the amount of water described in [Table 3](#).

35 **Table 3. Sevelamer Carbonate Powder Preparation Instructions**

Renvela Powder Packet Strength	Minimum amount of water for dose preparation (either ounces, mL or teaspoon/Tablespon)		
	ounces	mL	tsp/Tbsp
0.8 g	1	30	6 teaspoons/2 Tablespoons
2.4 g	2	60	4 Tablespoons

36
 37 Multiple packets may be mixed together with the appropriate amount of water. Patients
 38 should be instructed to stir the mixture vigorously (it does not dissolve) and drink the
 39 entire preparation within 30 minutes and resuspend the preparation right before drinking.

40 Based on clinical studies, the average prescribed daily dose of sevelamer carbonate is
 41 approximately 7.2 g per day.

42 **3 DOSAGE FORMS AND STRENGTHS**

43 Tablets: 800 mg white oval, film-coated, compressed tablets imprinted with “REVELA
 44 800”

45 Powder: 0.8 g and 2.4 g pale yellow powder packaged in an opaque, foil lined, heat
 46 sealed packet

47 **4 CONTRAINDICATIONS**

48 Renvela is contraindicated in patients with bowel obstruction.

49 **5 WARNINGS AND PRECAUTIONS**

50 **5.1 Gastrointestinal Adverse Events**

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

55

56 Cases of bowel obstruction and perforation have been reported with sevelamer use.

57

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

61 **5.2 Monitor Serum Chemistries**

62 Bicarbonate and chloride levels should be monitored.

63 **5.3 Monitor for Reduced Vitamins D, E, K (clotting factors) and Folic Acid**
64 **Levels**

65 In preclinical studies in rats and dogs, sevelamer hydrochloride, which contains the same
66 active moiety as sevelamer carbonate, reduced vitamins D, E, and K (coagulation
67 parameters) and folic acid levels at doses of 6-10 times the recommended human dose.

68 In short-term clinical trials, there was no evidence of reduction in serum levels of
69 vitamins. However, in a one-year clinical trial, 25-hydroxyvitamin D (normal range 10 to
70 55 ng/mL) fell from 39 ± 22 ng/mL to 34 ± 22 ng/mL ($p < 0.01$) with sevelamer
71 hydrochloride treatment. Most (approximately 75%) patients in sevelamer hydrochloride
72 clinical trials received vitamin supplements, which is typical of patients on dialysis.

73 **6 ADVERSE REACTIONS**

74 **6.1 Clinical Trials Experience**

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

78 There are limited data on the safety of Renvela. However, based on the fact that it
79 contains the same active ingredient as the hydrochloride salt, the adverse event profiles of
80 the two salts should be similar. In a cross-over study in hemodialysis patients with
81 treatment durations of eight weeks each and no washout the adverse reactions on
82 sevelamer carbonate tablets were similar to those reported for sevelamer hydrochloride.
83 In another cross-over study in hemodialysis patients, with treatment durations of four
84 weeks each and no washout between treatment periods, the adverse reactions on
85 sevelamer carbonate powder were similar to those reported for sevelamer hydrochloride.

86 In a parallel design study of sevelamer hydrochloride with treatment duration of
87 52 weeks, adverse reactions reported for sevelamer hydrochloride (n=99) were similar to
88 those reported for the active-comparator group (n=101). Overall adverse reactions
89 among those treated with sevelamer hydrochloride occurring in > 5% of patients
90 included: vomiting (22%), nausea (20%), diarrhea (19%), dyspepsia (16%), abdominal
91 pain (9%), flatulence (8%) and constipation (8%). A total of 27 patients treated with
92 sevelamer and 10 patients treated with comparator withdrew from the study due to
93 adverse reactions.

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

96 In one hundred and forty-three peritoneal dialysis patients studied for 12 weeks using
97 sevelamer hydrochloride, most adverse reactions were similar to adverse reactions
98 observed in hemodialysis patients. The most frequently occurring treatment emergent
99 serious adverse reaction was peritonitis (8 reactions in 8 patients [8%] in the sevelamer
100 group and 2 reactions in 2 patients [4%] on active-control). Thirteen patients (14%) in
101 the sevelamer group and 9 patients (20%) in the active-control group discontinued,
102 mostly for gastrointestinal adverse reactions. Patients on peritoneal dialysis should be
103 closely monitored to ensure the reliable use of appropriate aseptic technique with the
104 prompt recognition and management of any signs and symptoms associated with
105 peritonitis.

106 **6.2 Postmarketing Experience**

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

110 The following adverse reactions have been identified during post-approval use of
111 sevelamer hydrochloride, which has the same active moiety as sevelamer carbonate:
112 pruritus, rash, abdominal pain, fecal impaction, and uncommon cases of ileus, intestinal
113 obstruction, and intestinal perforation. Appropriate medical management should be given
114 to patients who develop constipation or have worsening of existing constipation to avoid
115 severe complications.

116 **7 DRUG INTERACTIONS**

117 Sevelamer carbonate has been studied in human drug-drug interaction studies with
118 warfarin and digoxin. Sevelamer hydrochloride, which contains the same active moiety
119 as sevelamer carbonate, has been studied in human drug-drug interaction studies with
120 ciprofloxacin, digoxin, warfarin, enalapril, metoprolol and iron.

121 7.1 Ciprofloxacin

122 In a study of 15 healthy subjects, a co-administered single dose of 2.8 grams of sevelamer
123 hydrochloride decreased the bioavailability of ciprofloxacin by approximately 50%.

124 7.2 Digoxin

125 In 19 healthy subjects receiving 2.4 grams of sevelamer hydrochloride three times a day
126 with meals for 2 days, sevelamer did not alter the pharmacokinetics of a single dose of
127 digoxin.

128 In 18 healthy subjects receiving 9.6 grams of sevelamer carbonate once daily with a meal,
129 sevelamer did not alter the pharmacokinetics of a single dose of digoxin.

130 7.3 Warfarin

131 In 14 healthy subjects receiving 2.4 g of sevelamer hydrochloride three times a day with
132 meals for two days sevelamer did not alter the pharmacokinetics of a single dose of
133 warfarin.

134 In 14 healthy subjects receiving 9.6 grams of sevelamer carbonate once daily with a meal,
135 sevelamer did not alter the pharmacokinetics of a single dose of warfarin.

136 7.4 Enalapril

137 In 28 healthy subjects a single 2.4 gram dose of sevelamer hydrochloride did not alter the
138 pharmacokinetics of a single dose of enalapril.

139 7.5 Metoprolol

140 In 31 healthy subjects a single 2.4 gram dose of sevelamer hydrochloride did not alter the
141 pharmacokinetics of a single dose of metoprolol.

142 7.6 Iron

143 In 23 healthy subjects, a single 2.8 gram dose of sevelamer hydrochloride did not alter
144 the absorption of a single oral dose of iron as 200 mg exsiccated ferrous sulfate tablet.

145 7.7 Other Concomitant Drug Therapy

146 There are no empirical data on avoiding drug interactions between Renvela and most
147 concomitant drugs. During postmarketing experience, very rare cases of increased
148 thyroid stimulating hormone (TSH) levels have been reported in patients co-administered
149 sevelamer hydrochloride and levothyroxine. Monitor TSH levels and signs of
150 hypothyroidism in patients receiving both medications.

151 When administering an oral medication where a reduction in the bioavailability of that
152 medication would have a clinically significant effect on its safety or efficacy, there is no
153 information that suggests a dosing regimen that would be universally appropriate for all

154 drugs. One may, however, administer the drug one hour before or three hours after
155 Renvela, and monitor blood levels of the drug. Patients taking anti-arrhythmic
156 medications for the control of arrhythmias and anti-seizure medications for the control of
157 seizure disorders were excluded from the clinical trials.

158 **8 USE IN SPECIFIC POPULATIONS**

159 **8.1 Pregnancy**

160 Pregnancy Category C: There are no adequate and well-controlled studies in pregnant
161 women. Sevelamer products should be used during pregnancy only if the potential
162 benefit justifies the potential risk to the fetus.

163 The effect of sevelamer hydrochloride on the absorption of vitamins and other nutrients
164 has not been studied in pregnant women. Requirements for vitamins and other nutrients
165 are increased in pregnancy. In pregnant rats given doses of sevelamer hydrochloride
166 during organogenesis, reduced or irregular ossification of fetal bones, probably due to a
167 reduced absorption of fat-soluble vitamin D, occurred at a dose approximately equal to
168 the maximum clinical trial dose of 13 g on a body surface area basis. In pregnant rabbits
169 given oral doses of sevelamer hydrochloride by gavage during organogenesis, an increase
170 of early resorptions occurred at dose approximately twice the maximum clinical trial dose
171 on a body surface area basis [*see Nonclinical Toxicology (13.2)*].

172 **8.2 Labor and Delivery**

173 No sevelamer hydrochloride treatment-related effects on labor and delivery were seen in
174 animal studies [*see Nonclinical Toxicology (13)*]. The effects of sevelamer carbonate on
175 labor and delivery in humans is unknown.

176 **8.4 Pediatric Use**

177 The safety and efficacy of Renvela has not been established in pediatric patients.

178 **8.5 Geriatric Use**

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

184 **10 OVERDOSAGE**

185 Sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate,
186 has been given to normal healthy volunteers in doses of up to 14 grams per day for eight
187 days with no adverse effects. In CKD patients on dialysis, the maximum dose studied
188 was 14 grams of sevelamer carbonate and 13 grams of sevelamer hydrochloride. There

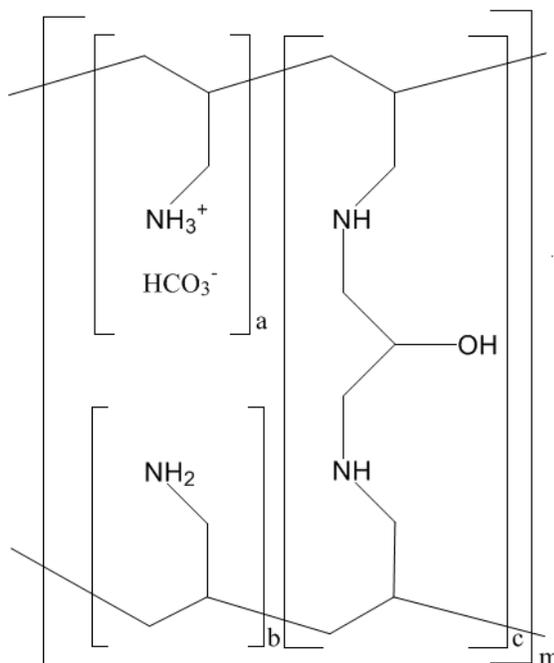
189 are no reports of overdose with sevelamer carbonate or sevelamer hydrochloride in
190 patients. Since sevelamer is not absorbed, the risk of systemic toxicity is low.

191 11 DESCRIPTION

192 The active ingredient in Renvela is sevelamer carbonate, a polymeric amine that binds
193 phosphate and is meant for oral administration. It was developed as a pharmaceutical
194 alternative to sevelamer hydrochloride (Renagel®). Sevelamer carbonate is an anion
195 exchange resin, with the same polymeric structure as sevelamer hydrochloride, in which
196 carbonate replaces chloride as the counterion. While the counterions differ for the two
197 salts, the polymer itself, the active moiety involved in phosphate binding, is the same.

198 Renvela (sevelamer carbonate) is known chemically as poly(allylamine-co-N,N'-diallyl-
199 1,3-diamino-2-hydroxypropane) carbonate salt. Sevelamer carbonate is hygroscopic, but
200 insoluble in water. The structure is represented in Figure 1.

201 **Figure 1. Chemical Structure of Sevelamer Carbonate**



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205 a, b = number of primary amine groups a + b = 9

206 c = number of crosslinking groups c = 1

207 m = large number to indicate extended polymer network

208

209 **Renvela® Tablets:** Each film-coated tablet of Renvela contains 800 mg of sevelamer
210 carbonate on an anhydrous basis. The inactive ingredients are hypromellose, diacetylated

211 monoglycerides, microcrystalline cellulose, sodium chloride and zinc stearate. The tablet
212 imprint contains iron oxide black ink.

213 **Renvela® Powder:** Each packet of Renvela Powder contains 0.8 g or 2.4 g of sevelamer
214 carbonate on an anhydrous basis. The inactive ingredients are natural and artificial citrus
215 flavor, propylene glycol alginate, sodium chloride, sucralose, and ferric oxide (yellow).

216 **12 CLINICAL PHARMACOLOGY**

217 Patients with chronic kidney disease (CKD) retain phosphorus and can develop
218 hyperphosphatemia. When the product of serum calcium and phosphorus concentrations
219 ($\text{Ca} \times \text{P}$) exceeds $55 \text{ mg}^2/\text{dL}^2$, there is an increased risk that ectopic calcification will
220 occur. Hyperphosphatemia plays a role in the development of secondary
221 hyperparathyroidism in renal insufficiency.

222 Treatment of hyperphosphatemia includes reduction in dietary intake of phosphate,
223 inhibition of intestinal phosphate absorption with phosphate binders, and removal of
224 phosphate with dialysis. Sevelamer carbonate taken with meals has been shown to
225 control serum phosphorus concentrations in patients with CKD who are on dialysis.

226 **12.1 Mechanism of Action**

227 Renvela contains sevelamer carbonate, a non-absorbed phosphate binding crosslinked
228 polymer, free of metal and calcium. It contains multiple amines separated by one carbon
229 from the polymer backbone. These amines exist in a protonated form in the intestine and
230 interact with phosphate molecules through ionic and hydrogen bonding. By binding
231 phosphate in the gastrointestinal tract and decreasing absorption, sevelamer carbonate
232 lowers the phosphate concentration in the serum (serum phosphorus).

233 **12.2 Pharmacodynamics**

234 In addition to effects on serum phosphorus levels, sevelamer hydrochloride has been
235 shown to bind bile acids *in vitro* and *in vivo* in experimental animal models. Bile acid
236 binding by ion exchange resins is a well-established method of lowering blood
237 cholesterol. Because sevelamer binds bile acids, it may interfere with normal fat
238 absorption and thus may reduce absorption of fat soluble vitamins such as A, D and K. In
239 clinical trials of sevelamer hydrochloride, both the mean total and LDL cholesterol
240 declined by 15-31%. This effect is observed after 2 weeks. Triglycerides, HDL
241 cholesterol and albumin did not change.

242 **12.3 Pharmacokinetics**

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

246 **13 NONCLINICAL TOXICOLOGY**

247 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

248 Standard lifetime carcinogenicity bioassays were conducted in mice and rats. Rats were
249 given sevelamer hydrochloride by diet at 0.3, 1, or 3 g/kg/day. There was an increased
250 incidence of urinary bladder transitional cell papilloma in male rats of the high dose
251 group (human equivalent dose twice the maximum clinical trial dose of 13 g). Mice
252 received dietary administration of sevelamer hydrochloride at doses of up to 9 g/kg/day
253 (human equivalent dose 3 times the maximum clinical trial dose). There was no
254 increased incidence of tumors observed in mice.

255 In an *in vitro* mammalian cytogenetic test with metabolic activation, sevelamer
256 hydrochloride caused a statistically significant increase in the number of structural
257 chromosome aberrations. Sevelamer hydrochloride was not mutagenic in the Ames
258 bacterial mutation assay.

259 Sevelamer hydrochloride did not impair the fertility of male or female rats in a dietary
260 administration study in which the females were treated from 14 days prior to mating
261 through gestation and the males were treated for 28 days prior to mating. The highest
262 dose in this study was 4.5 g/kg/day (human equivalent dose 3 times the maximum clinical
263 trial dose of 13 g).

264 **13.2 Developmental Toxicity**

265 In pregnant rats given dietary doses of 0.5, 1.5 or 4.5 g/kg/day of sevelamer
266 hydrochloride during organogenesis, reduced or irregular ossification of fetal bones,
267 probably due to a reduced absorption of fat-soluble vitamin D, occurred in mid- and high-
268 dose groups (human equivalent doses approximately equal to and 3-4 times the maximum
269 clinical trial dose of 13 g). In pregnant rabbits given oral doses of 100, 500 or 1000
270 mg/kg/day of sevelamer hydrochloride by gavage during organogenesis, an increase of
271 early resorptions occurred in the high-dose group (human equivalent dose twice the
272 maximum clinical trial dose).

273 **14 CLINICAL STUDIES**

274 The ability of sevelamer to control serum phosphorus in CKD patients on dialysis was
275 predominantly determined from the effects of the hydrochloride salt to bind phosphate.
276 Six clinical trials used sevelamer hydrochloride and three clinical trials used sevelamer
277 carbonate. The sevelamer hydrochloride studies include one double-blind, placebo-
278 controlled 2-week study (sevelamer N=24); two open-label, uncontrolled, 8-week studies
279 (sevelamer N=220) and three active-controlled open-label studies with treatment
280 durations of 8 to 52 weeks (sevelamer N=256). The sevelamer carbonate studies include
281 one double-blind, active-controlled, cross-over study with two 8-week treatment periods
282 using sevelamer carbonate tablets (N=79), one open-label, active-controlled, cross-over

283 study with two 4-week treatment periods using sevelamer carbonate powder (N=31) and
284 one randomized, parallel, open-label study using sevelamer carbonate powder (N=144)
285 dosed once daily or sevelamer hydrochloride tablets (N=73) dosed three times daily for
286 24 weeks. Six of the active-controlled studies are described here (three sevelamer
287 carbonate and three sevelamer hydrochloride studies).

288 **14.1 Cross-Over Study of Sevelamer Carbonate (Renvela[®]) 800 mg Tablets and** 289 **Sevelamer Hydrochloride (Renagel[®]) 800 mg Tablets**

290 Stage 5 CKD patients on hemodialysis were entered into a five-week sevelamer
291 hydrochloride run-in period and 79 patients received, in random order, sevelamer
292 carbonate 800 mg tablets and sevelamer hydrochloride 800 mg tablets for eight weeks
293 each, with no intervening washout. Study dose during the cross-over period was
294 determined based on the sevelamer hydrochloride dose during the run-in period on a
295 gram per gram basis. The phosphorus levels at the end of each of the two cross-over
296 periods were similar. Average actual daily dose was 6 g/day divided among meals for
297 both treatments. Thirty-nine of those completing the cross-over portion of the study were
298 entered into a two-week washout period during which patients were instructed not to take
299 any phosphate binders; this confirmed the activity of sevelamer in this study.

300 **14.2 Cross-Over Study of Sevelamer Carbonate (Renvela[®]) Powder and** 301 **Sevelamer Hydrochloride (Renagel[®]) Tablets**

302 Stage 5 CKD patients on hemodialysis were entered into a four-week sevelamer
303 hydrochloride run-in period and 31 patients received, in random order, sevelamer
304 carbonate powder and sevelamer hydrochloride tablets for four weeks each with no
305 intervening washout. Study dose during the cross-over period was determined based on
306 the sevelamer hydrochloride dose during the run-in period on a gram per gram basis. The
307 phosphorus levels at the end of each of the two cross-over periods were similar. Average
308 actual daily dose was 6.0 g/day divided among meals for sevelamer carbonate powder
309 and 6.4 g/day divided among meals for sevelamer hydrochloride tablets.

310 **14.3 Sevelamer Hydrochloride Versus Active-Control, Cross-Over Study in** 311 **Hemodialysis Patients**

312 Eighty-four CKD patients on hemodialysis who were hyperphosphatemic (serum
313 phosphorus > 6.0 mg/dL) following a two-week phosphate binder washout period were
314 randomized in a cross-over design to receive in random order sevelamer hydrochloride
315 and active-control for eight weeks each. Treatment periods were separated by a two-
316 week phosphate binder washout period. Patients started on treatment three times per day
317 with meals. Over each eight-week treatment period, at three separate time points the dose
318 of sevelamer hydrochloride could be titrated up to control serum phosphorus, the dose of
319 active-control could also be altered to attain phosphorus control. Both treatments
320 significantly decreased mean serum phosphorus by about 2 mg/dL ([Table 4](#)).

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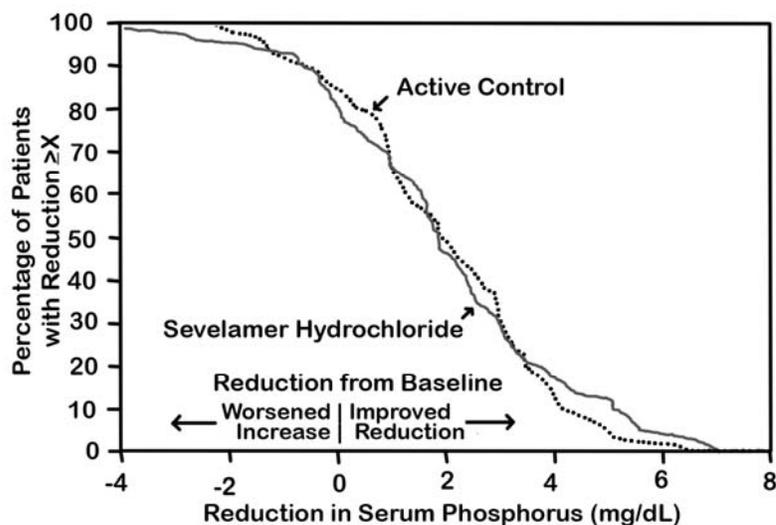
Table 4.
Mean Serum Phosphorus (mg/dL) at Baseline and Endpoint

	Sevelamer Hydrochloride (N=81)	Active Control (N=83)
Baseline at End of Washout	8.4	8.0
Endpoint	6.4	5.9
Change from Baseline at Endpoint (95% Confidence Interval)	-2.0* (-2.5, -1.5)	-2.1* (-2.6, -1.7)

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*p<0.0001, within treatment group comparison

325 **The distribution of responses is shown in Figure 2. The distributions are similar for**
 326 **sevelamer hydrochloride and active control. The median response is a reduction of**
 327 **about 2 mg/dL in both groups. About 50% of subjects have reductions between 1**
 328 **and 3 mg/dL. Figure 2. Percentage of patients (Y-axis) attaining a phosphorus**
 329 **reduction from baseline (mg/dL) at least as great as the value of the X-axis.**

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352 Average daily sevelamer hydrochloride dose at the end of treatment was 4.9 g (range of
 353 0.0 to 12.6 g).

354 **14.4 Sevelamer Hydrochloride Versus Active-Control in Hemodialysis Patients**

355 Two hundred CKD patients on hemodialysis who were hyperphosphatemic (serum
 356 phosphorus > 5.5 mg/dL) following a two-week phosphate binder washout period were
 357 randomized to receive sevelamer hydrochloride 800 mg tablets (N=99) or an active-
 358 control (N=101). At week 52, using last-observation-carried-forward, sevelamer and
 359 active-control both significantly decreased mean serum phosphorus (Table 5).

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Table 5.
Mean Serum Phosphorus (mg/dL) and Ion Product at Baseline and Change from Baseline to End of Treatment

	Sevelamer HCl (N=94)	Active- Control (N=98)
Phosphorus Baseline	7.5	7.3
Change from Baseline at Endpoint	-2.1	-1.8
Ca x Phosphorus Ion Product Baseline	70.5	68.4
Change from Baseline at Endpoint	-19.4	-14.2

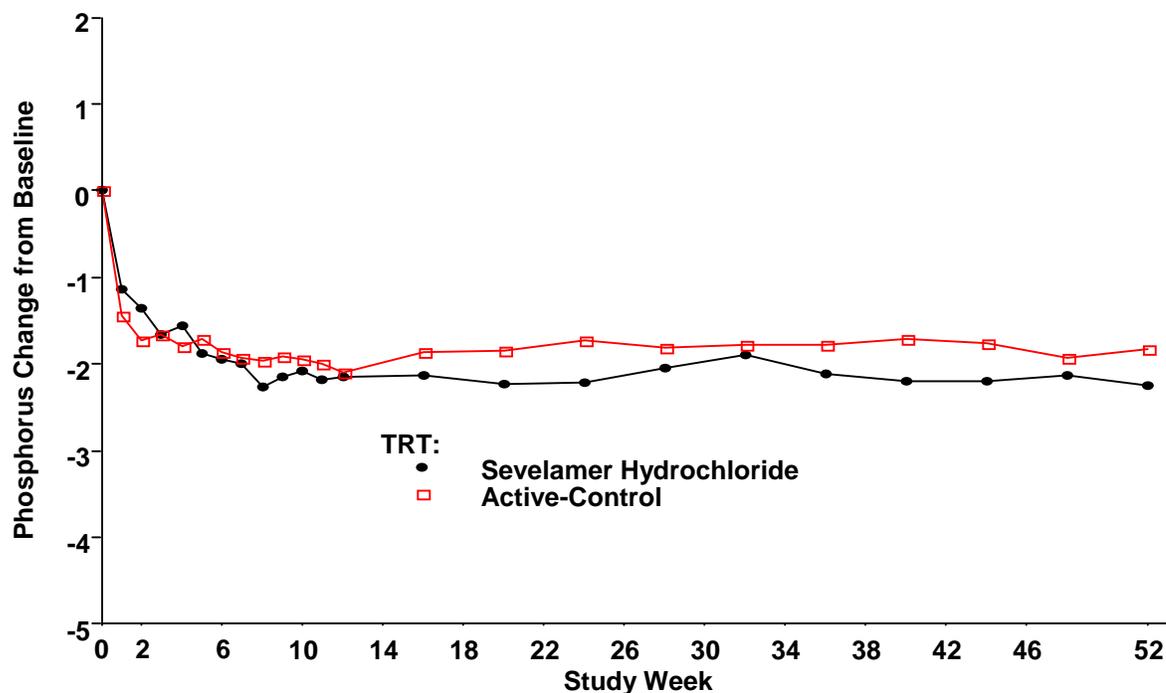
363

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

366 [Figure 3](#), a plot of the phosphorus change from baseline for the completers, illustrates the
367 durability of response for patients who are able to remain on treatment.

368
369

Figure 3. Mean Phosphorus Change from Baseline for Patients who Completed 52 Weeks of Treatment



370
371

372 Average daily sevelamer hydrochloride dose at the end of treatment was 6.5 g (range of
373 0.8 to 13 g).

374 **14.5 Sevelamer Hydrochloride Versus Active-Control in Peritoneal Dialysis** 375 **Patients**

376 One hundred and forty-three patients on peritoneal dialysis who were hyperphosphatemic
377 (serum phosphorus > 5.5 mg/dL) following a two-week phosphate binder washout period
378 were randomized to receive sevelamer hydrochloride (N=97) or active-control (N=46)
379 open label for 12 weeks. Average daily sevelamer hydrochloride dose at the end of
380 treatment was 5.9 g (range 0.8 to 14.3 g). Thirteen patients (14%) in the sevelamer group
381 and 9 patients (20%) in the active-control group discontinued, mostly for gastrointestinal
382 adverse reactions. There were statistically significant changes in serum phosphorus
383 ($p < 0.001$) for sevelamer hydrochloride (-1.6 mg/dL from baseline of 7.5 mg/dL), similar
384 to the active-control.

385 **14.6 Once a Day Versus Three Times a Day Dosing**

386 Stage 5 CKD patients on hemodialysis with a serum phosphate level of > 5.5 mg/dl after
387 washout from baseline therapies were randomized in a 2:1 ratio to receive either
388 sevelamer carbonate powder once-daily (N=144) or sevelamer hydrochloride as a tablet
389 with the dose divided three times per day (N=73) for 24 weeks. The initial dose for the

390 two groups was 4.8 g/day. At the end of the study, the total daily dose was 6.2 g/day of
391 sevelamer carbonate powder once daily and 6.7 g/day of sevelamer hydrochloride tablets
392 three times per day. A greater percentage of subjects on the once daily dose than three
393 times per day regimen discontinued therapy prematurely, 35% versus 15%. The reasons
394 for discontinuation were largely driven by adverse events and withdrawal of consent in
395 the once daily dosing regimen. Serum phosphate levels and calcium-phosphate product
396 were better controlled on the three times per day regimen than on the once daily regimen.
397 Mean serum phosphorus decreased 2.0 mg/dL for sevelamer carbonate powder once
398 daily and 2.9 mg/dL for sevelamer hydrochloride tablets three times per day.

399 **16 HOW SUPPLIED/STORAGE AND HANDLING**

400 Tablets: Renvela® 800 mg Tablets are supplied as white oval, film-coated, compressed
401 tablets, imprinted with “REVELA 800”, containing 800 mg of sevelamer carbonate on
402 an anhydrous basis, microcrystalline cellulose, hypromellose, diacetylated
403 monoglycerides, sodium chloride, and zinc stearate.

404 1 Bottle of 30 ct 800 mg Tablets (NDC 58468-0130-2)

405 1 Bottle of 270 ct 800 mg Tablets (NDC 58468-0130-1)

406 Powder: Renvela® for Oral Suspension is supplied as opaque, foil lined, heat sealed,
407 packets containing 0.8 g or 2.4 g of sevelamer carbonate on an anhydrous basis, natural
408 and artificial citrus flavor, propylene glycol alginate, sodium chloride, sucralose, and
409 ferric oxide (yellow).

410 1 Box (NDC 58468-0131-2) of 90 ct 2.4 g packets (NDC 58468-0131-1)

411 1 Box (NDC 58468-0132-2) of 90 ct 0.8 g packets (NDC 58468-0132-1)

412 1 Sample Box (NDC 58468-0131-4) of 90 ct 2.4 g packets (NDC 58468-0131-3)

413 1 Sample Box (NDC 58468-0131-5) of 15 ct 2.4 g packets (NDC 58468-0131-3)

414 **Storage:** Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

415 [See USP controlled room temperature]

416 Protect from moisture.

417 **17 PATIENT COUNSELING INFORMATION**

418 **17.1 Dosing**

419 Inform patients to take Renvela as directed with meals and adhere to their prescribed
420 diets.

421 For patients using an oral medication where a reduction in the bioavailability of that
422 medication would have a clinically significant effect on its safety or efficacy, advise the

423 patient to take the oral medication at least one hour before or three hours after Renvela.
 424 Blood levels of the oral medication should be monitored, if applicable, to determine if
 425 there is a significant interaction between the oral medication and Renvela.

426 For Renvela powder, brief the patient on preparation of the powder in water.

427 **Sevelamer Carbonate Powder Preparation Instructions**

428 The entire contents of each 0.8 or 2.4 g packet should be placed in a cup and mixed
 429 thoroughly with the amount of water described in [Table 6](#).

430 **Table 6. Sevelamer Carbonate Powder Preparation Instructions**

Renvela Powder Packet Strength	Minimum amount of water for dose preparation (either ounces, ml or teaspoon/Teaspoon)		
	ounces	mL	tsp/Tbsp
0.8 g	1	30	6 teaspoons/2 Tablespoons
2.4 g	2	60	4 Tablespoons

431
 432 Multiple packets may be mixed together with the appropriate amount of water. Patients
 433 should be instructed that the powder does not dissolve and therefore it should be stirred
 434 vigorously just before drinking. The entire preparation should be consumed within 30
 435 minutes.

436 **17.2 Adverse Reactions**

437 Renvela may cause constipation that if left untreated, may lead to severe complications.
 438 Patients should be cautioned to report new onset or worsening of existing constipation
 439 promptly to their physician.

440 Distributed by:

441 Genzyme Corporation

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