

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-318**

**LABELING**

## 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) ( 06/2009)

### INDICATIONS AND USAGE

- Renvela<sup>®</sup> 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

- The safety and efficacy of Renvela in patients with dysphagia, swallowing disorders, severe GI motility disorders including severe constipation, or major GI tract surgery have not been established. Uncommon cases of bowel obstruction and perforation have been reported. (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%). (6.1) 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](http://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: 06/2009

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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

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

15 **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

16

17 *Switching from Sevelamer Hydrochloride Tablets.* For patients switching from sevelamer  
18 hydrochloride tablets to sevelamer carbonate tablets or powder, use the same dose in  
19 grams. Further titration to the desired phosphorus levels may be necessary to achieve  
20 desired phosphorus levels. The highest daily dose of sevelamer carbonate studied was  
21 14 grams in CKD patients on dialysis.

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

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

28 **Table 2. Starting Dose for Dialysis Patients Switching From**  
 29 **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

30

31 *Dose Titration for All Patients Taking Renvela.* Titrate the Renvela dose by 0.8 g TID  
 32 with meals at two-week intervals as necessary with the goal of controlling serum  
 33 phosphorus within the target range.

34 **2.2 Sevelamer Carbonate Powder Preparation Instructions**

35 The entire contents of each 0.8 or 2.4 g packet should be placed in a cup and mixed  
 36 thoroughly with the amount of water described in Table 3.

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

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

38

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

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

44 **3 DOSAGE FORMS AND STRENGTHS**

45 Tablets: 800 mg white oval, film-coated, compressed tablets imprinted with "REVELA  
 46 800"

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

49 **4 CONTRAINDICATIONS**

50 Renvela is contraindicated in patients with bowel obstruction.

51 **5 WARNINGS AND PRECAUTIONS**

52 **5.1 Use Caution in Patients with Gastrointestinal Disorders**

53 The safety of Renvela has not been established in patients with dysphagia, swallowing  
54 disorders, severe gastrointestinal (GI) motility disorders including severe constipation, or  
55 major GI tract surgery. Uncommon cases of bowel obstruction and perforation have been  
56 reported.

57 **5.2 Monitor Serum Chemistries**

58 Bicarbonate and chloride levels should be monitored.

59 **5.3 Monitor for Reduced Vitamins D, E, K (clotting factors) and Folic Acid**  
60 **Levels**

61 In preclinical studies in rats and dogs, sevelamer hydrochloride, which contains the same  
62 active moiety as sevelamer carbonate, reduced vitamins D, E, and K (coagulation  
63 parameters) and folic acid levels at doses of 6-10 times the recommended human dose.  
64 In short-term clinical trials, there was no evidence of reduction in serum levels of  
65 vitamins. However, in a one-year clinical trial, 25-hydroxyvitamin D (normal range 10 to  
66 55 ng/mL) fell from  $39 \pm 22$  ng/mL to  $34 \pm 22$  ng/mL ( $p < 0.01$ ) with sevelamer  
67 hydrochloride treatment. Most (approximately 75%) patients in sevelamer hydrochloride  
68 clinical trials received vitamin supplements, which is typical of patients on dialysis.

69 **6 ADVERSE REACTIONS**

70 **6.1 Clinical Trials Experience**

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

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

82 In a parallel design study of sevelamer hydrochloride with treatment duration of  
83 52 weeks, adverse reactions reported for sevelamer hydrochloride (n=99) were similar to  
84 those reported for the active-comparator group (n=101). Overall adverse reactions  
85 among those treated with sevelamer hydrochloride occurring in > 5% of patients  
86 included: vomiting (22%), nausea (20%), diarrhea (19%), dyspepsia (16%), abdominal  
87 pain (9%), flatulence (8%) and constipation (8%). A total of 27 patients treated with

88 sevelamer and 10 patients treated with comparator withdrew from the study due to  
89 adverse reactions.

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

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

## 102 **6.2 Postmarketing Experience**

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

106  
107 The following adverse reactions have been identified during post-approval use of  
108 sevelamer hydrochloride, which has the same active moiety as sevelamer carbonate:  
109 pruritus, rash, abdominal pain, fecal impaction, and uncommon cases of ileus, intestinal  
110 obstruction, and intestinal perforation. Appropriate medical management should be given  
111 to patients who develop constipation or have worsening of existing constipation to avoid  
112 severe complications.

## 113 **7 DRUG INTERACTIONS**

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

### 118 **7.1 Ciprofloxacin**

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

### 121 **7.2 Digoxin**

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

125 In 18 healthy subjects receiving 9.6 grams of sevelamer carbonate once daily, sevelamer  
126 did not alter the pharmacokinetics of a single dose of digoxin.

### 127 **7.3 Warfarin**

128 In 14 healthy subjects receiving 2.4 g of sevelamer hydrochloride three times a day with  
129 meals sevelamer did not alter the pharmacokinetics of a single dose of warfarin.

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

### 132 **7.4 Enalapril**

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

### 135 **7.5 Metoprolol**

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

### 138 **7.6 Iron**

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

### 141 **7.7 Other Concomitant Drug Therapy**

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

147 When administering an oral medication where a reduction in the bioavailability of that  
148 medication would have a clinically significant effect on its safety or efficacy, there is no  
149 information that suggests a dosing regimen that would be universally appropriate for all  
150 drugs. One may, however, administer the drug one hour before or three hours after  
151 Renvela, and when important, monitor blood levels of the drug. Patients taking anti-  
152 arrhythmic medications for the control of arrhythmias and anti-seizure medications for  
153 the control of seizure disorders were excluded from the clinical trials.

## 154 **8 USE IN SPECIFIC POPULATIONS**

155 **8.1 Pregnancy**

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

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

168 **8.2 Labor and Delivery**

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

172 **8.4 Pediatric Use**

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

174 **8.5 Geriatric Use**

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

180 **10 OVERDOSAGE**

181 Sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate,  
182 has been given to normal healthy volunteers in doses of up to 14 grams per day for eight  
183 days with no adverse effects. In CKD patients on dialysis, the maximum dose studied  
184 was 14 grams of sevelamer carbonate and 13 grams of sevelamer hydrochloride. There  
185 are no reports of overdosage with sevelamer carbonate or sevelamer hydrochloride in  
186 patients. Since sevelamer is not absorbed, the risk of systemic toxicity is low.

187 **11 DESCRIPTION**

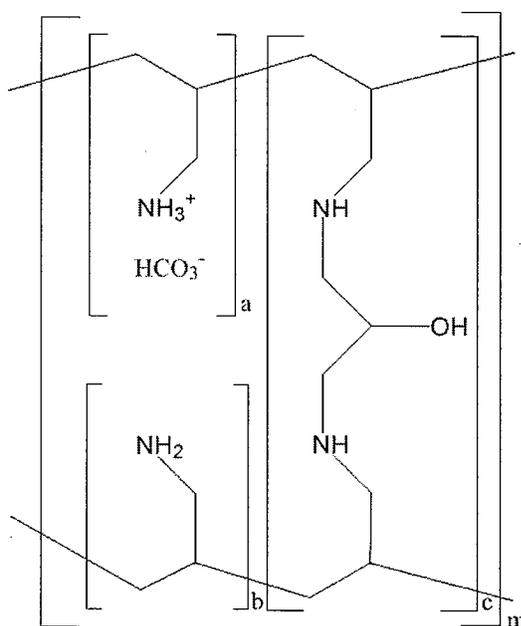
188 The active ingredient in Renvela is sevelamer carbonate, a polymeric amine that binds  
189 phosphate and is meant for oral administration. It was developed as a pharmaceutical

## PROPOSED TEXT OF THE LABELING OF THE DRUG

190 alternative to sevelamer hydrochloride (Renagel<sup>®</sup>). Sevelamer carbonate is an anion  
 191 exchange resin, with the same polymeric structure as sevelamer hydrochloride, in which  
 192 carbonate replaces chloride as the counterion. While the counterions differ for the two  
 193 salts, the polymer itself, the active moiety involved in phosphate binding, is the same.

194 Renvela (sevelamer carbonate) is known chemically as poly(allylamine-co-N,N'-diallyl-  
 195 1,3-diamino-2-hydroxypropane) carbonate salt. Sevelamer carbonate is hygroscopic, but  
 196 insoluble in water. The structure is represented in Figure 1.

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



199  
 200

201 a, b = number of primary amine groups      a + b = 9  
 202 c = number of crosslinking groups          c = 1  
 203 m = large number to indicate extended polymer network

204

205 **Renvela<sup>®</sup> Tablets:** Each film-coated tablet of Renvela contains 800 mg of sevelamer  
 206 carbonate on an anhydrous basis. The inactive ingredients are hypromellose, diacetylated  
 207 monoglycerides, microcrystalline cellulose, sodium chloride and zinc stearate. The tablet  
 208 imprint contains iron oxide black ink.

209 **Renvela<sup>®</sup> Powder:** Each packet of Renvela Powder contains 0.8 g or 2.4 g of sevelamer  
 210 carbonate on an anhydrous basis. The inactive ingredients are natural and artificial citrus  
 211 cream flavor, propylene glycol alginate, sodium chloride, sucralose, and ferric oxide  
 212 (yellow).

213 **12 CLINICAL PHARMACOLOGY**

214 Patients with chronic kidney disease (CKD) retain phosphorus and can develop  
215 hyperphosphatemia. When the product of serum calcium and phosphorus concentrations  
216 (Ca x P) exceeds 55 mg<sup>2</sup>/dL<sup>2</sup>, there is an increased risk that ectopic calcification will  
217 occur. Hyperphosphatemia plays a role in the development of secondary  
218 hyperparathyroidism in renal insufficiency.

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

223 **12.1 Mechanism of Action**

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

230 **12.2 Pharmacodynamics**

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

239 **12.3 Pharmacokinetics**

240 A mass balance study using <sup>14</sup>C-sevelamer hydrochloride, in 16 healthy male and female  
241 volunteers showed that sevelamer hydrochloride is not systemically absorbed. No  
242 absorption studies have been performed in patients with renal disease.

243 **13 NONCLINICAL TOXICOLOGY**

244 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

245 Standard lifetime carcinogenicity bioassays were conducted in mice and rats. Rats were  
246 given sevelamer hydrochloride by diet at 0.3, 1, or 3 g/kg/day. There was an increased  
247 incidence of urinary bladder transitional cell papilloma in male rats of the high dose  
248 group (human equivalent dose twice the maximum clinical trial dose of 13 g). Mice

249 received dietary administration of sevelamer hydrochloride at doses of up to 9 g/kg/day  
250 (human equivalent dose 3 times the maximum clinical trial dose). There was no  
251 increased incidence of tumors observed in mice.

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

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

### 261 **13.2 Developmental Toxicity**

262 In pregnant rats given dietary doses of 0.5, 1.5 or 4.5 g/kg/day of sevelamer  
263 hydrochloride during organogenesis, reduced or irregular ossification of fetal bones,  
264 probably due to a reduced absorption of fat-soluble vitamin D, occurred in mid- and high-  
265 dose groups (human equivalent doses approximately equal to and 3.4 times the maximum  
266 clinical trial dose of 13 g). In pregnant rabbits given oral doses of 100, 500 or 1000  
267 mg/kg/day of sevelamer hydrochloride by gavage during organogenesis, an increase of  
268 early resorptions occurred in the high-dose group (human equivalent dose twice the  
269 maximum clinical trial dose).

## 270 **14 CLINICAL STUDIES**

271 The ability of sevelamer to control serum phosphorus in CKD patients on dialysis was  
272 predominantly determined from the effects of the hydrochloride salt to bind phosphate.  
273 Six clinical trials used sevelamer hydrochloride and two clinical trials used sevelamer  
274 carbonate. The sevelamer hydrochloride studies include one double-blind, placebo-  
275 controlled 2-week study (sevelamer N=24); two open-label, uncontrolled, 8-week studies  
276 (sevelamer N=220) and three active-controlled open-label studies with treatment  
277 durations of 8 to 52 weeks (sevelamer N=256). The sevelamer carbonate studies include  
278 one double-blind, active-controlled, cross-over study with two 8-week treatment periods  
279 using sevelamer carbonate tablets (N=79) and one open-label, active-controlled, cross-  
280 over study with two 4-week treatment periods using sevelamer carbonate powder (N=31).  
281 Five of the active-controlled studies are described here (two sevelamer carbonate and  
282 three sevelamer hydrochloride studies).

283

284

285 **14.1 Cross-Over Study of Sevelamer Carbonate (Renvela<sup>®</sup>) 800 mg Tablets and**  
 286 **Sevelamer Hydrochloride (Renagel<sup>®</sup>) 800 mg Tablets**

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

297 **14.2 Cross-Over Study of Sevelamer Carbonate (Renvela<sup>®</sup>) Powder and**  
 298 **Sevelamer Hydrochloride (Renagel<sup>®</sup>) Tablets**

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

307 **14.3 Sevelamer Hydrochloride Versus Active-Control, Cross-Over Study in**  
 308 **Hemodialysis Patients**

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

318  
 319

**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

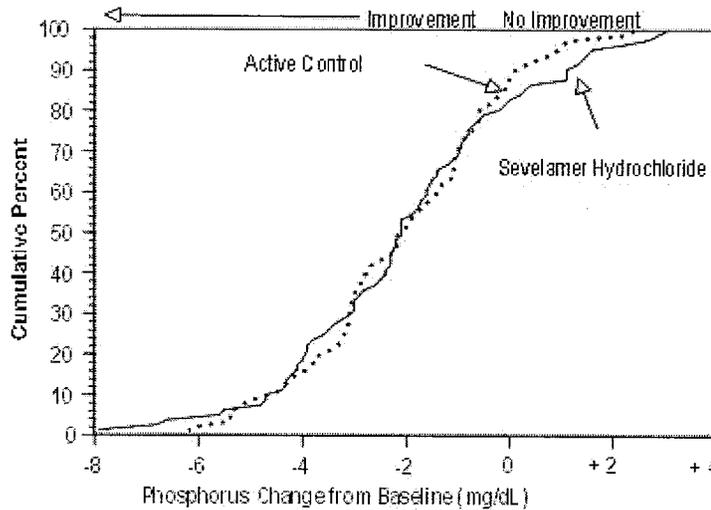
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Change from Baseline at Endpoint (95% Confidence Interval)	-2.0* (-2.5, -1.5)	-2.1* (-2.6, -1.7)
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\*p<0.0001, within treatment group comparison

320  
321  
322  
323  
324  
325

Figure 2. Cumulative percentage of patients (Y-axis) attaining a phosphorus change from baseline (mg/dL) at least as great as the value of the X-axis. A shift to the left of a curve indicates a better response.



326  
327  
328  
329  
330  
331  
332  
333  
334

335 Average daily sevelamer hydrochloride dose at the end of treatment was 4.9 g (range of  
336 0.0 to 12.6 g).

337 **14.4 Sevelamer Hydrochloride Versus Active-Control in Hemodialysis Patients**

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

343

Table 5.

344

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

345

	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

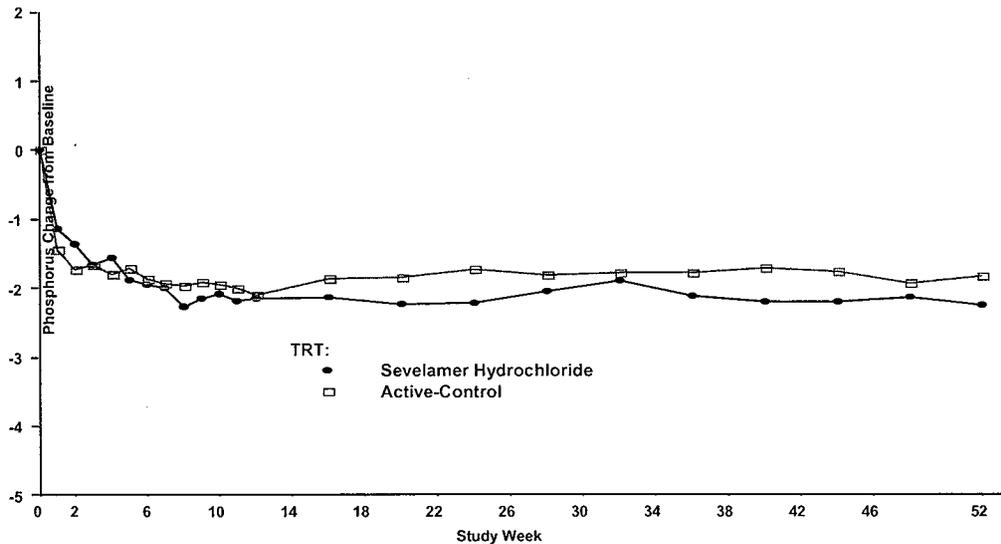
346

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

349 Figure 3, a plot of the phosphorus change from baseline for the completers, illustrates the  
350 durability of response for patients who are able to remain on treatment.

351  
352

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



353  
354

355 Average daily sevelamer hydrochloride dose at the end of treatment was 6.5 g (range of  
356 0.8 to 13 g).

#### 357 **14.5 Sevelamer Hydrochloride Versus Active-Control in Peritoneal Dialysis** 358 **Patients**

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

#### 368 **14.6 Once a Day Versus Three Times a Day Dosing** 369

370 Stage 5 CKD patients on hemodialysis with a serum phosphate level of > 5.5 mg/dl after  
371 washout from baseline therapies were randomized in a 2:1 ratio to receive either  
372 sevelamer carbonate powder once-daily (N=144) or sevelamer hydrochloride as a tablet  
373 with the dose divided TID (N=73) for 24 weeks. The initial dose for the two groups was  
374 4.8 g/day. At the end of the study, the total daily dose was  $6.2 \pm 2.6$  g/day of sevelamer

375 carbonate powder QD and  $6.7 \pm 3.0$  g/day of sevelamer hydrochloride tablets TID. A  
376 greater percentage of subjects on the once daily dose than TID regimen discontinued  
377 therapy prematurely, 35% versus 15%. The reasons for discontinuation were largely  
378 driven by adverse events and withdrawal of consent in the once daily dosing regimen.  
379 Serum phosphate levels and calcium-phosphate product were better controlled on the TID  
380 regimen than on the QD regimen. Mean serum phosphorus decreased  $2.0 \pm 1.8$  mg/dL  
381 for sevelamer carbonate powder QD and  $2.9 \pm 1.3$  mg/dL for sevelamer hydrochloride  
382 tablets TID.  
383

## 384 16 HOW SUPPLIED/STORAGE AND HANDLING

385 Tablets: Renvela<sup>®</sup> 800 mg Tablets are supplied as white oval, film-coated, compressed  
386 tablets, imprinted with "REVELA 800", containing 800 mg of sevelamer carbonate on  
387 an anhydrous basis, microcrystalline cellulose, hypromellose, diacetylated  
388 monoglycerides, sodium chloride, and zinc stearate.

389 1 Bottle of 30 ct 800 mg Tablets (NDC 58468-0130-2)

390 1 Bottle of 270 ct 800 mg Tablets (NDC 58468-0130-1)

391 Powder: Renvela<sup>®</sup> for Oral Suspension is supplied as opaque, foil lined, heat sealed,  
392 packets containing 0.8 g or 2.4 g of sevelamer carbonate on an anhydrous basis, natural  
393 and artificial citrus cream flavor, propylene glycol alginate, sodium chloride, sucralose,  
394 and ferric oxide (yellow).

395 1 Box (NDC 58468-0131-2) of 90 ct 2.4 g packets (NDC 58468-0131-1)

396 1 Box (NDC 58468-0132-2) of 90 ct 0.8 g packets (NDC 58468-0132-1)

397 1 Sample Box (NDC 58468-0131-4) of 90 ct 2.4 g packets (NDC 58468-0131-3)

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

399 [See USP controlled room temperature]

400 Protect from moisture.

401

## 402 17 PATIENT COUNSELING INFORMATION

### 403 17.1 Dosing

404 Inform patients to take Renvela as directed with meals and adhere to their prescribed  
405 diets.

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

**PROPOSED TEXT OF THE LABELING OF THE DRUG**

408 patient to take the drug at least one hour before or three hours after Renvela but blood  
409 tests may be necessary to determine if there is a significant interaction between the drugs.

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

411 **Sevelamer Carbonate Powder Preparation Instructions**

412 The entire contents of each 0.8 or 2.4 g packet should be placed in a cup and mixed  
413 thoroughly with the amount of water described in Table 3.

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

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

415

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

420 **17.2 Adverse Reactions**

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

424 Distributed by:

425 Genzyme Corporation

426 500 Kendall Street

427 Cambridge, MA 02142 USA