

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-127

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

Initial U.S. Approval: 2000

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 is one to two 800 mg tablets three times per day with meals. (2)
- Adjust by one tablet per meal in two week intervals as needed to obtain serum phosphorus target (3.5 to 5.5 mg/dL). (2)

DOSAGE FORMS AND STRENGTHS

- Tablets: 800 mg (3)

CONTRAINDICATIONS

- In patients with hypophosphatemia or 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. Caution should be exercised when Renvela is used in patients with these GI disorders. (5.1)

ADVERSE REACTIONS

- Most frequently occurring adverse reactions for Renvela in a short term (8-week crossover) study were: nausea (3%) and vomiting (3%). (6.1). 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 and or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- In a normal volunteer study, sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, decreased the bioavailability of ciprofloxacin by approximately 50%. (7.1)
- In normal volunteer studies, sevelamer hydrochloride did not alter the pharmacokinetics of a single dose of digoxin, warfarin, enalapril, metoprolol, and 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, the drug should be administered at least one hour before or three hours after Renvela, or the physician should consider monitoring blood levels of the drug. (7.7)

See 17 for PATIENT COUNSELING INFORMATION

Revised: [10/2007]

FULL PRESCRIBING INFORMATION: CONTENTS*

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

1 **1. INDICATIONS AND USAGE**

2 Renvela™¹ (sevelamer carbonate) is indicated for the control of serum phosphorus in
 3 patients with chronic kidney disease (CKD) on dialysis. The safety and efficacy of
 4 Renagel in CKD patients who are not on dialysis have not been studied.

5 **2. DOSAGE AND ADMINISTRATION**

6 Because of the rapid disintegration of the carbonate salt tablet and its rapid reaction with
 7 the hydrochloric acid in the stomach, the dosing of Renvela is anticipated to be similar to
 8 that of the hydrochloride salt.

9 *Patients Not Taking a Phosphate Binder.* The recommended starting dose of Renvela is
 10 800 to 1600 mg, which can be administered as one or two Renvela 800 mg Tablets, with
 11 meals based on serum phosphorus level. Table 1 provides recommended starting doses
 12 of Renvela for patients not taking a phosphate binder.

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

Serum Phosphorus	Renvela 800 mg
> 5.5 and < 7.5 mg/dL	1 tablet three times daily with meals
≥ 7.5 and < 9.0 mg/dL	2 tablets three times daily with meals
≥ 9.0 mg/dL	2 tablets three times daily with meals

14 *Patients Switching from Sevelamer Hydrochloride.* For patients switching from
 15 sevelamer hydrochloride, sevelamer carbonate should be prescribed on a gram per gram
 16 basis. Further titration to the desired phosphate levels may be necessary. The highest
 17 daily dose of sevelamer carbonate studied was 14 grams in CKD patients on dialysis.

18 *Patients Switching From Calcium Acetate.* In a study in 84 CKD patients on
 19 hemodialysis, a similar reduction in serum phosphorus was seen with equivalent doses
 20 (approximately mg for mg) of sevelamer hydrochloride and calcium acetate. Table 2
 21 gives recommended starting doses of Renvela based on a patient's current calcium
 22 acetate dose.

23 **Table 2. Starting Dose for Dialysis Patients Switching From Calcium Acetate to**
 24 **Renvela**

Calcium Acetate 667 mg (Tablets per meal)	Renvela 800 mg (Tablets per meal)
1 tablet	1 tablet
2 tablets	2 tablets
3 tablets	3 tablets

25 *Dose Titration for All Patients Taking Renvela.* The dose should be increased or
 26 decreased by one tablet per meal at two week intervals, as necessary, with the goal of
 27 controlling serum phosphorus within the target range of 3.5 mg/dL to 5.5 mg/dL.

28 3. DOSAGE FORMS AND STRENGTHS

29 800 mg white oval, film-coated, compressed tablets imprinted with "Renvela 800"

30 4. CONTRAINDICATIONS

31 Renvela is contraindicated in patients with hypophosphatemia or bowel obstruction.

32 5. WARNINGS AND PRECAUTIONS

33 5.1 Use Caution in Patients with Gastrointestinal Disorders

34 The safety of Renvela has not been established in patients with dysphagia, swallowing
 35 disorders, severe gastrointestinal (GI) motility disorders including severe constipation, or
 36 major GI tract surgery. Use caution in patients with these GI disorders.

37 5.2 Monitor Serum Chemistries

38 Bicarbonate and chloride levels should be monitored.

39 5.3 Monitor for Reduced Vitamins D, E, K (clotting factors) and Folic Acid 40 Levels

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

49 6. ADVERSE REACTIONS

50 **6.1 Clinical Trials Experience**

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

54

55 There are limited data on the safety of Renvela. However, based on it contains the same
56 active ingredient as the hydrochloride salt, the adverse event profiles of the two salts
57 should be similar. In a cross-over study in hemodialysis patients with treatment durations
58 of eight weeks each and no washout the adverse reactions on sevelamer carbonate were
59 similar to those reported for sevelamer hydrochloride.

60

61 In a parallel design study of sevelamer hydrochloride with treatment duration of
62 52 weeks, adverse reactions reported for sevelamer hydrochloride (n=99) were similar to
63 those reported for the active comparator group (n=101). Overall adverse reactions among
64 those treated with sevelamer hydrochloride occurring in > 5% of patients included:
65 vomiting (22%), nausea (20%), diarrhea (19%), dyspepsia (16%), abdominal pain (9%),
66 flatulence (8%) and constipation (8%). A total of 27 patients treated with sevelamer and
67 10 patients treated with comparator withdrew from the study due to adverse reactions.

68

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

71 In one hundred and forty-three peritoneal dialysis patients studied for 8 weeks using
72 sevelamer hydrochloride, most adverse reactions were similar to adverse reactions
73 observed in hemodialysis patients. The most frequently occurring treatment emergent
74 serious adverse reaction was peritonitis (8 reactions in 8 patients [8%] in the sevelamer
75 group and 2 reactions in 2 patients [4%] on active control. Thirteen patients (14%) in the
76 sevelamer group and 9 patients (20%) in the active control group discontinued, mostly for
77 gastrointestinal adverse reactions. Patients on PD should be closely monitored to ensure
78 the reliable use of appropriate aseptic technique with the prompt recognition and
79 management of any signs and symptoms associated with peritonitis.

80 **6.2 Postmarketing Experience**

81 The following adverse reactions have been identified during post-approval use of
82 sevelamer hydrochloride, which has the same active moiety as sevelamer carbonate:
83 pruritis, rash, abdominal pain, fecal impaction, and uncommon cases of ileus, intestinal

84 obstruction, and intestinal perforation. Appropriate medical management should be given
85 to patients who develop constipation or have worsening of existing constipation to avoid
86 severe complications.

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

90 7. DRUG INTERACTIONS

91 No drug interaction studies have been performed with sevelamer carbonate. Sevelamer
92 hydrochloride, which contains the same active moiety as sevelamer carbonate, has been
93 studied in human drug-drug interaction studies with ciprofloxacin, digoxin, warfarin,
94 enalapril, metoprolol and iron.

95 7.1 Ciprofloxacin

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

98 7.2 Digoxin

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

102 7.3 Warfarin

103 In 14 healthy subjects receiving 2.4 grams of sevelamer hydrochloride three times a day
104 with meals for 2 days, sevelamer did not alter the pharmacokinetics of a single dose of
105 warfarin.

106 7.4 Enalapril

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

109 7.5 Metoprolol

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

112 7.6 Iron

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

115 **7.7 Other Concomitant Drug Therapy**

116 There are no empirical data on avoiding drug interactions between Renvela and most
117 concomitant drugs. However, when administering an oral medication where a reduction
118 in the bioavailability of that medication would have a clinically significant effect on its
119 safety or efficacy, the drug should be administered at least one hour before or three hours
120 after Renvela, or the physician should consider monitoring blood levels of the drug.
121 Patients taking anti-arrhythmic medications for the control of arrhythmias and anti-
122 seizure medications for the control of seizure disorders were excluded from the clinical
123 trials. Special precautions should be taken when prescribing Renvela to patients also
124 taking these medications.

125 **8. USE IN SPECIFIC POPULATIONS**

126 **8.1 Pregnancy**

127 Pregnancy Category C: The effect of sevelamer hydrochloride on the absorption of
128 vitamins and other nutrients has not been studied in pregnant women. Requirements for
129 vitamins and other nutrients are increased in pregnancy. In pregnant rats given doses of
130 sevelamer hydrochloride during organogenesis, reduced or irregular ossification of fetal
131 bones, probably due to a reduced absorption of fat-soluble vitamin D, occurred. In
132 pregnant rabbits given oral doses of sevelamer hydrochloride by gavage during
133 organogenesis, an increase of early resorptions occurred. [See *NONCLINICAL*
134 *TOXICOLOGY (13.1)*]

135 **8.2 Labor and Delivery**

136 No sevelamer hydrochloride treatment-related effects on labor and delivery were seen in
137 animal studies. The effects of sevelamer carbonate on labor and delivery on humans is
138 unknown. [See *NONCLINICAL TOXICOLOGY (13.1)*]

139 **8.4 Pediatric Use**

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

141 **8.5 Geriatric Use**

142 Clinical studies of Renvela did not include sufficient numbers of subjects aged 65 and
143 over to determine whether they respond differently from younger subjects. Other reported

144 clinical experience has not identified differences in responses between the elderly and
145 younger patients. In general, dose selection for an elderly patient should be cautious,
146 usually starting at the low end of the dosing range.

147

148 **10. OVERDOSAGE**

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

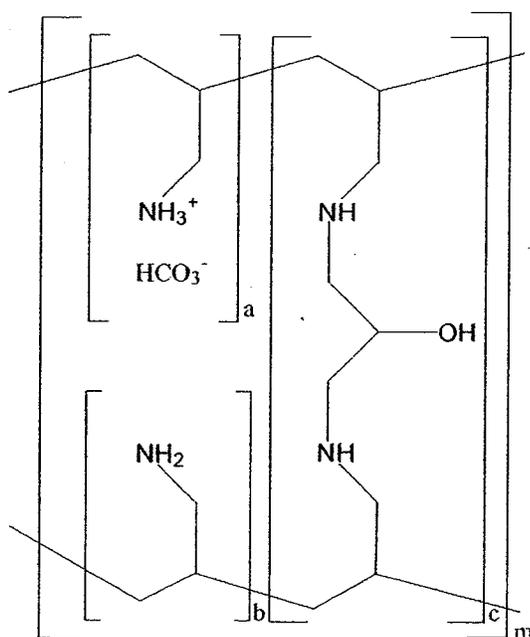
155 **11. DESCRIPTION**

156 The active ingredient in Renvela is sevelamer carbonate, a polymeric amine that binds
157 phosphate and is meant for oral administration. It was developed as a pharmaceutical
158 alternative to sevelamer hydrochloride (Renagel®). Sevelamer carbonate is an anion
159 exchange resin with the same polymeric structure as sevelamer hydrochloride in which
160 carbonate replaces chloride as the counterion. While the counterions differ for the two
161 salts, the polymer itself, the active moiety, is the same.

162 Renvela (sevelamer carbonate) is known chemically as poly (allylamine-co-N,N'-diallyl-
163 1,3-diamino-2-hydroxypropane) carbonate salt. Sevelamer carbonate is hygroscopic, but
164 insoluble in water. The structure is represented below:

165 Chemical Structure of Sevelamer Carbonate

166



167

168

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

170 c = number of crosslinking groups c = 1

171 m = large number to indicate extended polymer network

172

173 **Renvela™ Tablets:** Each film-coated tablet of Renvela contains 800 mg of sevelamer
 174 carbonate on an anhydrous basis. The inactive ingredients are hypromellose, diacetylated
 175 monoglycerides, microcrystalline cellulose, sodium chloride and zinc stearate. The tablet
 176 imprint contains iron oxide black ink.

177 12. CLINICAL PHARMACOLOGY

178 Patients with chronic kidney disease (CKD) retain phosphorus and can develop
 179 hyperphosphatemia. When the product of serum calcium and phosphorus concentrations
 180 (Ca x P) exceeds 55 mg²/dL², there is an increased risk that ectopic calcification will
 181 occur. Hyperphosphatemia plays a role in the development of secondary
 182 hyperparathyroidism in renal insufficiency.

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

187 **12.1 Mechanism of Action**

188 Renvela contains sevelamer carbonate, a non-absorbed phosphate binding crosslinked
189 polymer, free of metal and calcium. It contains multiple amines separated by one carbon
190 from the polymer backbone. These amines exist in a protonated form in the intestine and
191 interact with phosphate molecules through ionic and hydrogen bonding. By binding
192 phosphate in the dietary tract and decreasing absorption, sevelamer carbonate lowers the
193 phosphate concentration in the serum.

194 **12.2 Pharmacodynamics**

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

203 **12.3 Pharmacokinetics**

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

207 **13. NONCLINICAL TOXICOLOGY**

208 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

216 In an *in vitro* mammalian cytogenetic test with metabolic activation, sevelamer
217 hydrochloride caused a statistically significant increase in the number of structural

218 chromosome aberrations. Sevelamer hydrochloride was not mutagenic in the Ames
219 bacterial mutation assay.

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

225 In pregnant rats given dietary doses of 0.5, 1.5 or 4.5 g/kg/day of sevelamer
226 hydrochloride during organogenesis, reduced or irregular ossification of fetal bones,
227 probably due to a reduced absorption of fat-soluble vitamin D, occurred in mid- and high-
228 dose groups (human equivalent doses less than the maximum clinical trial dose of 13 g).
229 In pregnant rabbits given oral doses of 100, 500 or 1000 mg/kg/day of sevelamer
230 hydrochloride by gavage during organogenesis, an increase of early resorptions occurred
231 in the high-dose group (human equivalent dose twice the maximum clinical trial dose).

232 14. CLINICAL STUDIES

233 The ability of sevelamer to control serum phosphorus in CKD patients on dialysis was
234 predominantly determined from the effects of the hydrochloride salt to bind phosphate.
235 Six clinical trials used sevelamer hydrochloride and one clinical trial used sevelamer
236 carbonate. The sevelamer hydrochloride studies include one double-blind, placebo-
237 controlled 2-week study (sevelamer N=24); two open-label, uncontrolled, 8-week studies
238 (sevelamer N=220) and three active-controlled open-label studies with treatment
239 durations of 8 to 52 weeks (sevelamer N=256). The sevelamer carbonate study was a
240 double-blind, active controlled, cross-over study in hemodialysis patients with two 8-
241 week treatment periods (N=79). Four of the active-controlled studies are described here
242 (one sevelamer carbonate and three sevelamer hydrochloride studies).

243 14.1 Cross-Over Study of Sevelamer Carbonate (Renvela™) 800 mg Tablets and 244 Sevelamer Hydrochloride (Renagel®) 800 mg Tablets

245 Stage 5 CKD patients on hemodialysis were entered into a five-week sevelamer
246 hydrochloride run-in period and 79 patients received, in random order, sevelamer
247 carbonate 800 mg tablets and sevelamer hydrochloride 800 mg tablets for eight weeks
248 each, with no intervening washout. Study dose during the cross-over period was
249 determined based on the sevelamer hydrochloride dose during the run-in period on a

250 gram per gram basis. The phosphate levels at the end of each of the two cross-over
 251 periods were similar. Average actual daily dose was 6 g/day for both treatments. Thirty-
 252 nine of those completing the cross-over portion of the study were entered into a two-week
 253 washout period during which patients were instructed not to take any phosphate binders;
 254 this confirmed the activity of sevelamer in this study.

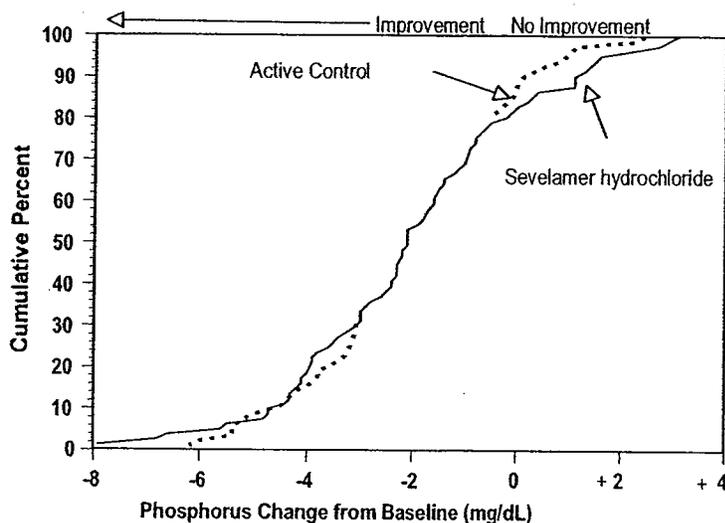
255 **14.2 Sevelamer Hydrochloride Versus Active-Control, Cross-Over Study in**
 256 **Hemodialysis Patients**

257 Eighty-four CKD patients on hemodialysis who were hyperphosphatemic (serum
 258 phosphorus > 6.0 mg/dL) following a two-week phosphate binder washout period were
 259 randomized in a crossover design to receive in random order sevelamer hydrochloride
 260 and active comparator for eight weeks each. Treatment periods were separated by a two-
 261 week phosphate binder washout period. Patients started on treatment three times per day
 262 with meals. Over each eight-week treatment period, at three separate time points the dose
 263 of sevelamer hydrochloride could be titrated up to control serum phosphorus, the dose of
 264 active control could also be altered to attain phosphate control. Both treatments
 265 significantly decreased mean serum phosphorus by about 2 mg/dL. (Table 3)
 266

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

267 *p <0.0001, within treatment group comparison

268 **Figure 1: Cumulative percent of patients (Y-axis) attaining a phosphorus change**
 269 **from baseline (mg/dL) at least as great as the value of the X-axis. A shift to the left of**
 270 **a curve indicates a better response.**



271

272 Average daily sevelamer hydrochloride dose at the end of treatment was 4.9 g (range of
 273 0.0 to 12.6 g).

274 **14.3 Sevelamer Hydrochloride versus Active-Control in Hemodialysis Patients**

275 Two hundred CKD patients on hemodialysis who were hyperphosphatemic (serum
 276 phosphorus >5.5 mg/dL) following a two-week phosphate binder washout period were
 277 randomized to receive sevelamer hydrochloride 800 mg tablets (N=99) or an active
 278 control (N=101). At week 52, using last-observation-carried-forward, sevelamer and
 279 control both significantly decreased mean serum phosphorus (Table 4).

280

Table 4:

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

	Sevelamer HCl (N=94)	Active Control (N=98)

PROPOSED TEXT OF THE LABELING OF THE DRUG

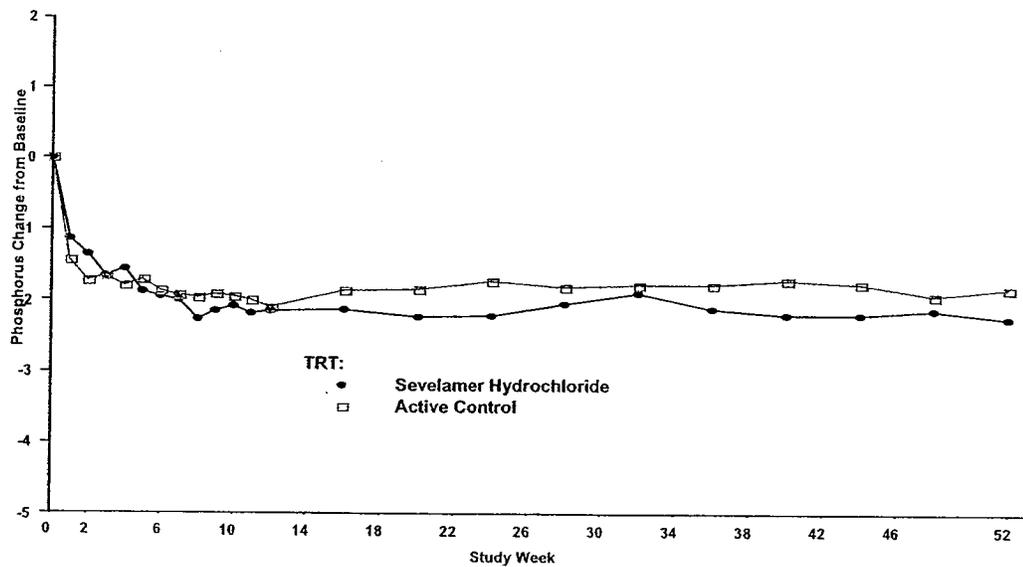
	Sevelamer HCl (N=94)	Active Control (N=98)
Phosphorus Baseline	7.5	7.3
Change from Baseline at Endpoint	-2.1	-1.8
Ca x Phosphorus Ion Product Baseline	70.5	68.4
Change from Baseline at Endpoint	-19.4	-14.2

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

285

286 Figure 2, a plot of the phosphorus change from baseline for the completers, illustrates the
 287 durability of response for patients who are able to remain on treatment.

288 **Figure 2: Mean Phosphorus Change from Baseline for Patients who Completed**
 289 **52 weeks of Treatment**



290
 291

292 Average daily sevelamer hydrochloride dose at the end of treatment was 6.5 g (range of
 293 0.8 to 13 g).

294 **14.4 Sevelamer Hydrochloride versus Active Control in Peritoneal Dialysis**
295 **Patients**

296 One hundred and forty-three patients on peritoneal dialysis who were hyperphosphatemic
297 (serum phosphorus > 5.5 mg/dL) following a two-week phosphate binder washout period
298 were randomized to receive Renagel (N=97) or active control (N=46) open label for 12
299 weeks. Average daily sevelamer hydrochloride dose at the end of treatment was 5.9 g
300 (range 0.8 to 14.3 g). Thirteen patients (14%) in the sevelamer group and 9 patients
301 (20%) in the active control discontinued, mostly for gastrointestinal adverse reactions.
302 There were statistically significant changes in serum phosphorus ($p < 0.001$) for
303 sevelamer hydrochloride (-1.6 mg/dL from baseline of 7.5 mg/dL), similar to the active
304 control.

305 **16. HOW SUPPLIED/STORAGE AND HANDLING**

306 Renvela™ 800 mg Tablets are supplied as white oval, film-coated, compressed tablets,
307 imprinted with “Renvela 800”, containing 800 mg of sevelamer carbonate on an
308 anhydrous basis, microcrystalline cellulose, hypromellose, diacetylated monoglycerides,
309 sodium chloride, and zinc stearate. Renvela 800 mg Tablets are packaged in 500cc
310 bottles of 270 tablets.

311 1 Bottle of 30 ct 800 mg Tablets (NDC XXX-XXXX-X).

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

313 [See USP controlled room temperature]

314 Protect from moisture.

315 Shelf life is 24 months.

316 **17. PATIENT COUNSELING INFORMATION**

317 **17.1 Dosing Recommendations**

318 The prescriber should inform patients to take Renvela with meals and adhere to their
319 prescribed diets. Instructions should be given on concomitant medications that should be
320 dosed apart from Renvela.

321 **17.2 Adverse Reactions**

PROPOSED TEXT OF THE LABELING OF THE DRUG

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

325 Distributed by:

326 Genzyme Corporation

327 500 Kendall Street

328 Cambridge, MA 02142 USA

329 ¹Trademark of Genzyme Corporation

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