

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

Renegel (sevelamer hydrochloride) Tablet for Oral use
Initial U.S. Approval: 2000

INDICATIONS AND USAGE

- Renegel[®] 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 or two 800 mg or two to four 400 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 and 400 mg (3)

CONTRAINDICATIONS

- In patients with hypophosphatemia or bowel obstruction. (4)

WARNINGS AND PRECAUTIONS

- The safety and efficacy of Renegel 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 Renegel is used in patients with these GI disorders. (5.1)

ADVERSE REACTIONS

- The most common reasons for discontinuing treatment were gastrointestinal adverse reactions. (6.1)
- In a parallel design study, of 12 weeks duration, treatment emergent adverse reactions to Renegel Tablets in peritoneal dialysis patients included dyspepsia (12%), peritonitis (8%), diarrhea (5%), nausea (5%), constipation (4%), pruritus (4%), abdominal distension (3%), vomiting (3%), fatigue (3%), anorexia (3%), and arthralgia (3%). (6.1)
- Similar reactions at similar rates occurred in hemodialysis and peritoneal dialysis patients. (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

- Decreases 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)
- During postmarketing experience, very rare cases of increased TSH levels have been reported in patients co-administered sevelamer hydrochloride and levothyroxine. Closer monitoring of TSH levels is therefore recommended in patients receiving both medications. (7.7)
- 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 Renegel, or the physician should consider monitoring blood levels of the drug. (7.7)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 11/2007

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1 **1. INDICATIONS AND USAGE**

2 RENAGEL^{®1} (sevelamer hydrochloride) is indicated for the control of serum phosphorus
 3 in 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 *Patients Not Taking a Phosphate Binder.* The recommended starting dose of Renagel is
 7 800 to 1600 mg, which can be administered as one or two 800 mg Renagel[®] Tablets or
 8 two to four 400 mg Renagel[®] Tablets, with meals based on serum phosphorus level.
 9 Table 1 provides recommended starting doses of Renagel for patients not taking a
 10 phosphate binder.

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

Serum Phosphorus	Renagel [®] 800 mg	Renagel [®] 400 mg
> 5.5 and < 7.5 mg/dL	1 tablet three times daily with meals	2 tablets three times daily with meals
≥ 7.5 and < 9.0 mg/dL	2 tablets three times daily with meals	3 tablets three times daily with meals
≥ 9.0 mg/dL	2 tablets three times daily with meals	4 tablets three times daily with meals

12 *Patients Switching From Calcium Acetate.* In a study in 84 CKD patients on
 13 hemodialysis, a similar reduction in serum phosphorus was seen with equivalent doses
 14 (approximately mg for mg) of Renagel and calcium acetate. [Table 2](#) gives recommended
 15 starting doses of Renagel based on a patient's current calcium acetate dose.

16 **Table 2. Starting Dose for Dialysis Patients Switching From Calcium Acetate to**
 17 **Renagel**

Calcium Acetate 667 mg (Tablets per meal)	Renagel® 800 mg (Tablets per meal)	Renagel® 400 mg (Tablets per meal)
1 tablet	1 tablet	2 tablets
2 tablets	2 tablets	3 tablets
3 tablets	3 tablets	5 tablets

18 *Dose Titration for All Patients Taking Renagel.* Dosage should be adjusted based on the
 19 serum phosphorus concentration with a goal of lowering serum phosphorus to 5.5 mg/dL
 20 or less. The dose may be increased or decreased by one tablet per meal at two week
 21 intervals as necessary. Table 3 gives a dose titration guideline. The average dose in a
 22 Phase 3 trial designed to lower serum phosphorus to 5.0 mg/dL or less was approximately
 23 three Renagel 800 mg tablets per meal. The maximum average daily Renagel dose
 24 studied was 13 grams.

25 **Table 3. Dose Titration Guideline**

Serum Phosphorus	Renagel® Dose
>5.5 mg/dL	Increase 1 tablet per meal at 2 week intervals
3.5 - 5.5 mg/dL	Maintain current dose
<3.5 mg/dL	Decrease 1 tablet per meal

26 **3. DOSAGE FORMS AND STRENGTHS**

27 800 mg and 400 mg Tablets.

28 **4. CONTRAINDICATIONS**

29 Renagel is contraindicated in patients with hypophosphatemia or bowel obstruction.

30 **5. WARNINGS AND PRECAUTIONS**

31 **5.1 Use Caution in Patients with Gastrointestinal Disorders**

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

35 **5.2 Monitor Serum Chemistries**

36 Bicarbonate and chloride levels should be monitored.

37 **5.3 Monitor for Reduced Vitamins D, E, K (clotting factors) and Folic Acid**
38 **Levels**

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

47 **6. ADVERSE REACTIONS**

48 **6.1 Clinical Trials Experience**

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

52 In a parallel design study of sevelamer hydrochloride with treatment duration of
53 52 weeks, adverse reactions reported for sevelamer hydrochloride ($n=99$) were similar to
54 those reported for the active-control group ($n=101$). Overall adverse reactions among
55 those treated with sevelamer hydrochloride occurring in $> 5\%$ of patients included:
56 vomiting (22%), nausea (20%), diarrhea (19%), dyspepsia (16%), abdominal pain (9%),
57 flatulence (8%) and constipation (8%). A total of 27 patients treated with sevelamer and
58 10 patients treated with comparator withdrew from the study due to adverse reactions.

59 Based on studies of 8-52 weeks, the most common reason for withdrawal from Renagel
60 was gastrointestinal adverse reactions (3-16%).

61 In one hundred and forty-three peritoneal dialysis patients studied for 12 weeks most
62 adverse reactions were similar to adverse reactions observed in hemodialysis patients.
63 The most frequently occurring treatment emergent serious adverse reaction was
64 peritonitis (8 reactions in 8 patients [8%] in the sevelamer group and 2 reactions in 2
65 patients [4%] on active-control). Thirteen patients (14%) in the sevelamer group and 9
66 patients (20%) in the active-control group discontinued, mostly for gastrointestinal
67 adverse reactions. Patients on peritoneal dialysis should be closely monitored to ensure
68 the reliable use of appropriate aseptic technique with the prompt recognition and
69 management of any signs and symptoms associated with peritonitis.

70 **6.2 Postmarketing Experience**

71 The following adverse reactions have been identified during post-approval use of
72 sevelamer hydrochloride (Renagel®): pruritus, rash, abdominal pain, fecal impaction and
73 uncommon cases of ileus, intestinal obstruction, and intestinal perforation. Appropriate
74 medical management should be given to patients who develop constipation or have
75 worsening of existing constipation to avoid severe complications.

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

79 **7. DRUG INTERACTIONS**

80 Renagel has been studied in human drug-drug interaction studies with ciprofloxacin,
81 digoxin, warfarin, enalapril, metoprolol and iron.

82 **7.1 Ciprofloxacin**

83 In a study of 15 healthy subjects, a co-administered single dose of 7 Renagel capsules
84 (approximately 2.8 g) decreased the bioavailability of ciprofloxacin by approximately
85 50%.

86 **7.2 Digoxin**

87 In 19 healthy subjects receiving 6 Renagel capsules three times a day with meals for 2
88 days, Renagel did not alter the pharmacokinetics of a single dose of digoxin.

89 **7.3 Warfarin**

90 In 14 healthy subjects receiving 6 Renagel capsules three times a day with meals for 2
91 days, Renagel did not alter the pharmacokinetics of a single dose of warfarin.

92 7.4 Enalapril

93 In 28 healthy subjects a single dose of 6 Renagel capsules did not alter the
94 pharmacokinetics of a single dose of enalapril.

95 7.5 Metoprolol

96 In 31 healthy subjects a single dose of 6 Renagel capsules did not alter the
97 pharmacokinetics of a single dose of metoprolol.

98 7.6 Iron

99 In 23 healthy subjects, a single dose of 7 Renagel capsules did not alter the absorption of
100 a single oral dose of iron as 200 mg exsiccated ferrous sulfate tablet.

101 7.7 Other Concomitant Drug Therapy

102 There are no empirical data on avoiding drug interactions between Renagel[®] and most
103 concomitant drugs. During postmarketing experience, very rare cases of increased
104 thyroid stimulating hormone (TSH) levels have been reported in patients co-administered
105 sevelamer hydrochloride and levothyroxine. Closer monitoring of TSH levels is
106 therefore recommended in patients receiving both medications.

107 When administering an oral medication where a reduction in the bioavailability of that
108 medication would have a clinically significant effect on its safety or efficacy, the drug
109 should be administered at least one hour before or three hours after Renagel, or the
110 physician should consider monitoring blood levels of the drug. Patients taking anti-
111 arrhythmic medications for the control of arrhythmias and anti-seizure medications for
112 the control of seizure disorders were excluded from the clinical trials. Special
113 precautions should be taken when prescribing Renagel to patients also taking these
114 medications.

115 8. USE IN SPECIFIC POPULATIONS**116 8.1 Pregnancy**

117 Pregnancy Category C: The effect of Renagel on the absorption of vitamins and other
118 nutrients has not been studied in pregnant women. Requirements for vitamins and other
119 nutrients are increased in pregnancy. In pregnant rats given doses of Renagel during
120 organogenesis, reduced or irregular ossification of fetal bones, probably due to a reduced
121 absorption of fat-soluble vitamin D, occurred. In pregnant rabbits given oral doses of

122 Renagel by gavage during organogenesis, an increase of early resorptions occurred. [See
123 *NONCLINICAL TOXICOLOGY (13.1)*]

124 **8.2 Labor and Delivery**

125 No Renagel treatment-related effects on labor and delivery were seen in animal studies.
126 The effects of Renagel on labor and delivery in humans are not known. [See
127 *NONCLINICAL TOXICOLOGY (13.1)*]

128 **8.4 Pediatric Use**

129 The safety and efficacy of Renagel has not been established in pediatric patients.

130 **8.5 Geriatric Use**

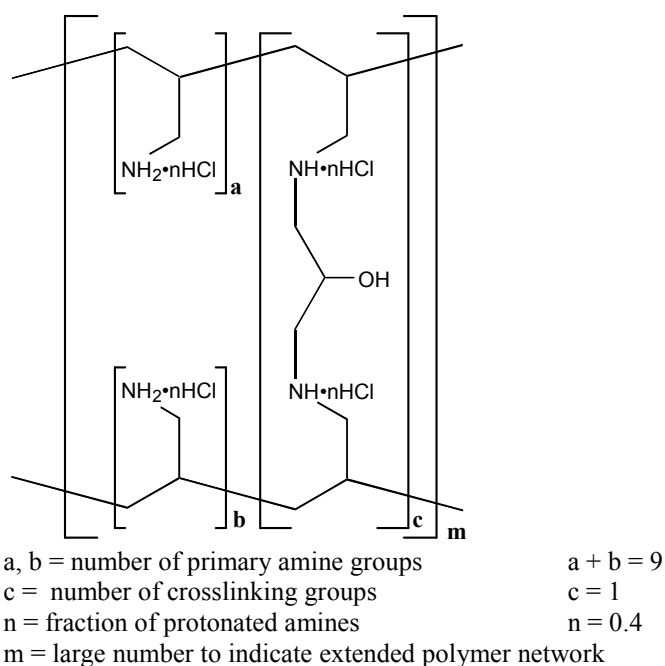
131 Clinical studies of Renagel did not include sufficient numbers of subjects aged 65 and
132 over to determine whether they respond differently from younger subjects. Other
133 reported clinical experience has not identified differences in responses between the
134 elderly and younger patients. In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

136 **10. OVERDOSAGE**

137 Renagel has been given to normal healthy volunteers in doses of up to 14 grams per day
138 for eight days with no adverse effects. Renagel has been given in average doses up to
139 13 grams per day to hemodialysis patients. There are no reports of overdosage with
140 Renagel in patients. Since Renagel is not absorbed, the risk of systemic toxicity is low.

141 **11. DESCRIPTION**

142 The active ingredient in Renagel Tablets is sevelamer hydrochloride, a polymeric amine
 143 that binds phosphate and is meant for oral administration. Sevelamer hydrochloride is
 144 poly(allylamine hydrochloride) crosslinked with epichlorohydrin in which forty percent
 145 of the amines are protonated. It is known chemically as poly(allylamine-co-N,N'-diallyl-
 146 1,3-diamino-2-hydroxypropane) hydrochloride. Sevelamer hydrochloride is hydrophilic,
 147 but insoluble in water. The structure is represented in Figure 1.

148 **Figure 1. Chemical Structure of Sevelamer Hydrochloride**

149 The primary amine groups shown in the structure are derived directly from
 150 poly(allylamine hydrochloride). The crosslinking groups consist of two secondary amine
 151 groups derived from poly(allylamine hydrochloride) and one molecule of
 152 epichlorohydrin.

153 **Renagel[®] Tablets:** Each film-coated tablet of Renagel contains either 800 mg or 400 mg
 154 of sevelamer hydrochloride on an anhydrous basis. The inactive ingredients are
 155 hypromellose, diacetylated monoglyceride, colloidal silicon dioxide, and stearic acid.
 156 The tablet imprint contains iron oxide black ink.

157 12. CLINICAL PHARMACOLOGY

158 Patients with chronic kidney disease (CKD) on dialysis retain phosphorus and can
159 develop hyperphosphatemia. High serum phosphorus can precipitate serum calcium
160 resulting in ectopic calcification. When the product of serum calcium and phosphorus
161 concentrations ($\text{Ca} \times \text{P}$) exceeds $55 \text{ mg}^2/\text{dL}^2$, there is an increased risk that ectopic
162 calcification will occur. Hyperphosphatemia plays a role in the development of
163 secondary hyperparathyroidism in renal insufficiency.

164 Treatment of hyperphosphatemia includes reduction in dietary intake of phosphate,
165 inhibition of intestinal phosphate absorption with phosphate binders, and removal of
166 phosphate with dialysis. Renagel taken with meals has been shown to decrease serum
167 phosphorus concentrations in patients with CKD who are on dialysis.

168 12.1 Mechanism of Action

169 Renagel contains sevelamer hydrochloride, a non-absorbed binding crosslinked polymer.
170 It contains multiple amines separated by one carbon from the polymer backbone. These
171 amines exist in a protonated form in the intestine and interact with phosphate molecules
172 through ionic and hydrogen bonding. By binding phosphate in the dietary tract and
173 decreasing absorption, sevelamer hydrochloride lowers the phosphate concentration in
174 the serum.

175 12.2 Pharmacodynamics

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

184 12.3 Pharmacokinetics

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

188 **13. NONCLINICAL TOXICOLOGY**

189 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

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

206 In pregnant rats given dietary doses of 0.5, 1.5 or 4.5 g/kg/day of sevelamer
207 hydrochloride during organogenesis, reduced or irregular ossification of fetal bones,
208 probably due to a reduced absorption of fat-soluble vitamin D, occurred in mid- and high-
209 dose groups (human equivalent doses less than the maximum clinical trial dose of 13 g).

210 In pregnant rabbits given oral doses of 100, 500 or 1000 mg/kg/day of sevelamer
211 hydrochloride by gavage during organogenesis, an increase of early resorptions occurred
212 in the high-dose group (human equivalent dose twice the maximum clinical trial dose).

213 **14. CLINICAL STUDIES**

214 The ability of Renagel to lower serum phosphorus in CKD patients on dialysis was
 215 demonstrated in six clinical trials: one double-blind placebo controlled 2-week study
 216 (Renagel N=24); two open-label uncontrolled 8-week studies (Renagel N=220) and three
 217 active-controlled open-label studies with treatment durations of 8 to 52 weeks (Renagel
 218 N=256). Three of the active-controlled studies are described here. One is a crossover
 219 study with two 8-week periods comparing Renagel to an active-control. The second is a
 220 52-week parallel study comparing Renagel with active-control. The third is a 12-week
 221 parallel study comparing Renagel and active-control in peritoneal dialysis patients.

222 **14.1 Active-Control, Cross-Over Study in Hemodialysis Patients**

223 Eighty-four CKD patients on hemodialysis who were hyperphosphatemic (serum
 224 phosphorus > 6.0 mg/dL) following a two-week phosphate binder washout period
 225 received Renagel and active-control for eight weeks each in random order. Treatment
 226 periods were separated by a two-week phosphate binder washout period. Patients started
 227 on treatment three times per day with meals. Over each eight-week treatment period, at
 228 three separate time points the dose of Renagel could be titrated up 1 capsule or tablet per
 229 meal (3 per day) to control serum phosphorus, the dose of active-control could also be
 230 altered to attain phosphate control. Both treatments significantly decreased mean serum
 231 phosphorus by about 2 mg/dL (Table 4).

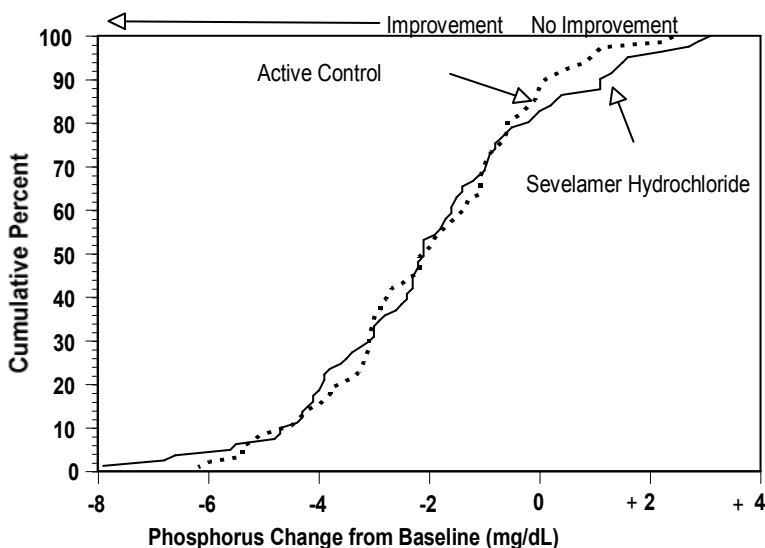
Table 4.		
Mean Serum Phosphorus (mg/dL) at Baseline and Endpoint		
	Renagel® (N=81)	Active-Control (N=83)
Baseline at End of Washout	8.4	8.0
Change from Baseline at Endpoint (95% Confidence Interval)	-2.0* (-2.5, -1.5)	-2.1* (-2.6, -1.7)

232 *p<0.0001, within treatment group comparison

233 [Figure 2](#) shows that the proportion of patients achieving a given level of serum
 234 phosphorus lowering is similar in the two treatment groups. Median decrease in
 235 phosphorus was 2 mg/dL on each treatment.

236 **Figure 2. Cumulative percent of patients (Y-axis) attaining a phosphorus change**
 237 **from baseline at least as great as the value of the X-axis. A shift to the left of a curve**
 238 **indicates a better response.**

239



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

241 **14.2 Active-Control, Parallel Study in Hemodialysis Patients**

242 Two hundred CKD patients on hemodialysis who were hyperphosphatemic (serum
 243 phosphorus >5.5 mg/dL) following a two-week phosphate binder washout period were
 244 randomized to receive Renagel 800 mg tablets (N=99) or an active-control (N=101). The
 245 two treatments produced similar decreases in serum phosphorus. At week 52, using last-
 246 observation-carried-forward, Renagel and active-control both significantly decreased
 247 mean serum phosphorus (Table 5).

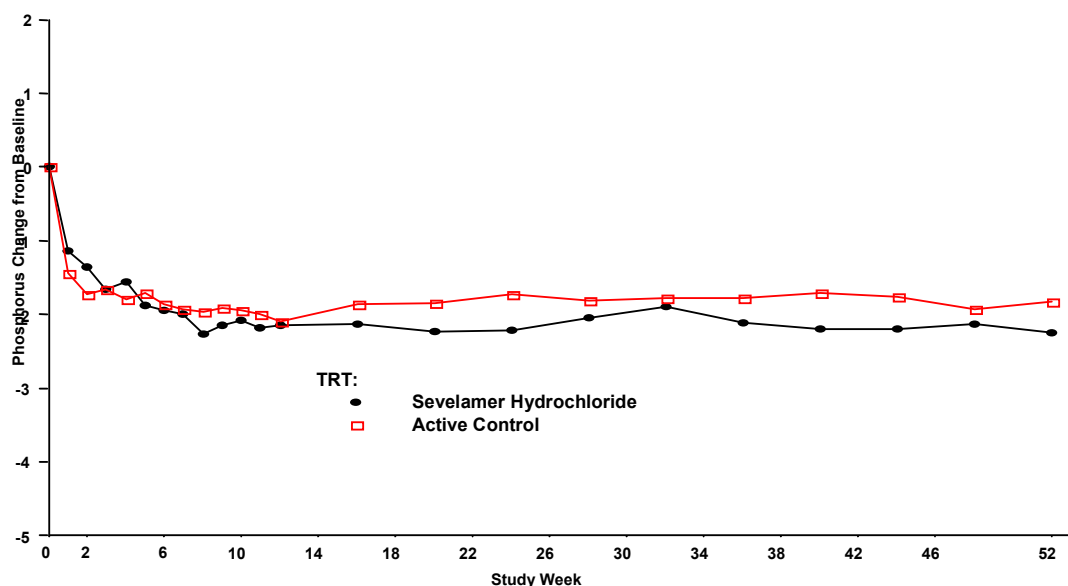
Table 5. Mean Serum Phosphorus (mg/dL) and Ion Product at Baseline and Change from Baseline to End of Treatment		
	Renagel [®] (N=94)	Active-Control (N=98)
Phosphorus Baseline	7.5	7.3

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

248 Sixty-one percent of Renagel patients and 73% of the control patients completed the full
249 52 weeks of treatment.

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

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



254
255

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

257 14.3 Active-Control, Parallel Study in Peritoneal Dialysis Patients

258 One hundred and forty-three patients on peritoneal dialysis who were hyperphosphatemic
259 (serum phosphorus > 5.5 mg/dL) following a two-week phosphate binder washout period
260 were randomized to receive Renagel® (N=97) or active-control (N=46) open label for 12
261 weeks. Average daily Renagel dose at the end of treatment was 5.9 g (range 0.8 to 14.3
262 g). There were statistically significant changes in serum phosphorus (p<0.001) for
263 Renagel (-1.6 mg/dL from baseline of 7.5 mg/dL), similar to the active-control.

264 16. HOW SUPPLIED/STORAGE AND HANDLING

265 Renagel[®] 800 mg Tablets are supplied as oval, film-coated, compressed tablets, imprinted
266 with “RENAGEL 800” containing 800 mg of sevelamer hydrochloride on an anhydrous
267 basis, hypromellose, diacetylated monoglyceride, colloidal silicon dioxide, and stearic
268 acid. Renagel[®] 800 mg Tablets are packaged in bottles of 180 tablets.

269 Renagel[®] 400 mg Tablets are supplied as oval, film-coated, compressed tablets, imprinted
270 with “RENAGEL 400” containing 400 mg of sevelamer hydrochloride on an anhydrous
271 basis, hypromellose, diacetylated monoglyceride, colloidal silicon dioxide, and stearic
272 acid. Renagel[®] 400 mg Tablets are packaged in bottles of 360 tablets.

273 1 Bottle of 30 ct 800 mg Tablets (NDC 58468-0021-3)

274 1 Bottle of 180 ct 800 mg Tablets (NDC 58468-0021-1)

275 1 Bottle of 360 ct 400 mg Tablets (NDC 58468-0020-1)

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

277 Do not use Renagel[®] after the expiration date on the bottle.

278 [See USP controlled room temperature]

279 Protect from moisture.

280 **17 PATIENT COUNSELING INFORMATION**

281 **17.1 Dosing Recommendations**

282 The prescriber should inform patients to take Renagel with meals and adhere to their
283 prescribed diets. Instructions should be given on concomitant medications that should be
284 dosed apart from Renagel.

285 **17.2 Adverse Reactions**

286 Renagel may cause constipation that if left untreated, may lead to severe complications.
287 Patients should be cautioned to report new onset or worsening of existing constipation
288 promptly to their physician.

289 Distributed by:

290 Genzyme Corporation

291 500 Kendall Street

292 Cambridge, MA 02142 USA

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