

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

Renagel® (sevelamer hydrochloride) Tablets for oral use
Initial U.S. Approval: 2000

INDICATIONS AND USAGE

- Renagel 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 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 Renagel 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 Renagel 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 8 weeks duration, treatment emergent adverse reactions to Renagel 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 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)
- 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 Renagel, or the physician should consider monitoring blood levels of the drug. (7.7)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 10/2007

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PROPOSED TEXT OF THE LABELING OF THE DRUG

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.

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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 events reported for sevelamer hydrochloride (n=99) were similar to
54 those reported for the active comparator group (n=101). Overall adverse events 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%).

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61 In one hundred and forty-three peritoneal dialysis patients studied for 8 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 PD should be closely monitored to ensure the reliable use
68 of appropriate aseptic technique with the prompt recognition and management of any
69 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[®]): pruritis, 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.

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

110 **8. USE IN SPECIFIC POPULATIONS**

111 **8.1 Pregnancy**

112 Pregnancy Category C: The effect of Renagel on the absorption of vitamins and other
113 nutrients has not been studied in pregnant women. Requirements for vitamins and other
114 nutrients are increased in pregnancy. In pregnant rats given doses of Renagel during
115 organogenesis, reduced or irregular ossification of fetal bones, probably due to a reduced
116 absorption of fat-soluble vitamin D, occurred. In pregnant rabbits given oral doses of
117 Renagel by gavage during organogenesis, an increase of early resorptions occurred. [See
118 *NONCLINICAL TOXICOLOGY (13.1)*]

119 **8.2 Labor and Delivery**

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

123 **8.4 Pediatric Use**

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

125 **8.5 Geriatric Use**

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

131 **10. OVERDOSAGE**

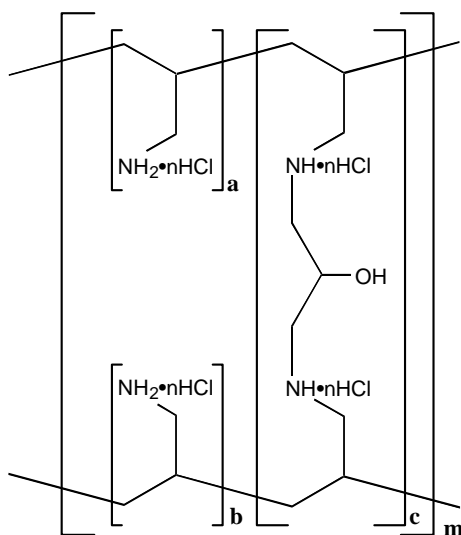
132 Renagel has been given to normal healthy volunteers in doses of up to 14 grams per day
133 for eight days with no adverse effects. Renagel has been given in average doses up to
134 13 grams per day to hemodialysis patients. There are no reports of overdosage with
135 Renagel in patients. Since Renagel is not absorbed, the risk of systemic toxicity is low.

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136 **11. DESCRIPTION**

137 The active ingredient in Renagel Tablets is sevelamer hydrochloride, a polymeric amine
138 that binds phosphate and is meant for oral administration. Sevelamer hydrochloride is
139 poly(allylamine hydrochloride) crosslinked with epichlorohydrin in which forty percent
140 of the amines are protonated. It is known chemically as poly(allylamine-co-N,N'-diallyl-
141 1,3-diamino-2-hydroxypropane) hydrochloride. Sevelamer hydrochloride is hydrophilic,
142 but insoluble in water. The structure is represented below:

143 Chemical Structure of Sevelamer Hydrochloride



a, b = number of primary amine groups a + b = 9
c = number of crosslinking groups c = 1
n = fraction of protonated amines n = 0.4
m = large number to indicate extended polymer network

144 The primary amine groups shown in the structure are derived directly from
145 poly(allylamine hydrochloride). The crosslinking groups consist of two secondary amine
146 groups derived from poly(allylamine hydrochloride) and one molecule of
147 epichlorohydrin.

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

152 **12. CLINICAL PHARMACOLOGY**

153 Patients with chronic kidney disease (CKD) on dialysis retain phosphorus and can
154 develop hyperphosphatemia. High serum phosphorus can precipitate serum calcium
155 resulting in ectopic calcification. When the product of serum calcium and phosphorus
156 concentrations (Ca x P) exceeds 55 mg²/dL², there is an increased risk that ectopic
157 calcification will occur. Hyperphosphatemia plays a role in the development of
158 secondary hyperparathyroidism in renal insufficiency.

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

163 **12.1 Mechanism of Action**

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

170 **12.2 Pharmacodynamics**

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

179 **12.3 Pharmacokinetics**

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

183 **13. NONCLINICAL TOXICOLOGY**

184 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

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

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

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

208 **14. CLINICAL STUDIES**

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

217 **14.1 Active-Control, Crossover Study in Hemodialysis Patients**

218 Eighty-four CKD patients on hemodialysis who were hyperphosphatemic (serum
219 phosphorus > 6.0 mg/dL) following a two-week phosphate binder washout period
220 received Renagel and active control for eight weeks each in random order. Treatment
221 periods were separated by a two-week phosphate binder washout period. Patients started
222 on treatment three times per day with meals. Over each eight-week treatment period, at
223 three separate time points the dose of Renagel could be titrated up 1 capsule or tablet per
224 meal (3 per day) to control serum phosphorus, the dose of active control could also be
225 altered to attain phosphate control. Both treatments significantly decreased mean serum
226 phosphorus by about 2 mg/dL (Table 5).

	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)

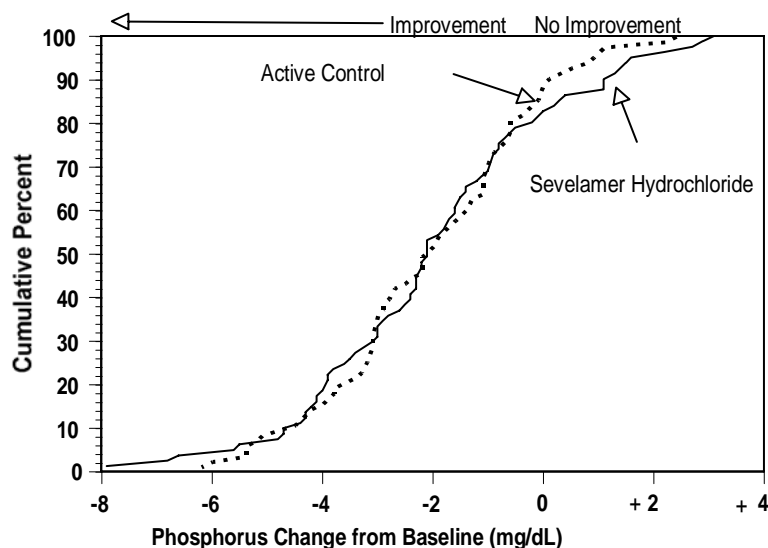
227 *p <0.0001, within treatment group comparison

228 Figure 1 shows that the proportion of patients achieving a given level of serum
229 phosphorus lowering is similar in the two treatment groups. Median decrease in
230 phosphorus was 2 mg/dL on each treatment.

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231 **Figure 1. Cumulative percent of patients (Y-axis) attaining a phosphorus change**
 232 **from baseline at least as great as the value of the X-axis. A shift to the left of a curve**
 233 **indicates a better response.**

234



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

236 **14.2 Active-Control, Parallel Study in Hemodialysis Patients**

237 Two hundred CKD patients on hemodialysis who were hyperphosphatemic (serum
 238 phosphorus >5.5 mg/dL) following a two-week phosphate binder washout period were
 239 randomized to receive Renagel 800 mg tablets (N=99) or an active control (N=101). The
 240 two treatments produced similar decreases in serum phosphorus. At week 52, using last-
 241 observation-carried-forward, Renagel and control both significantly decreased mean
 242 serum phosphorus (Table 6).

Table 6. 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

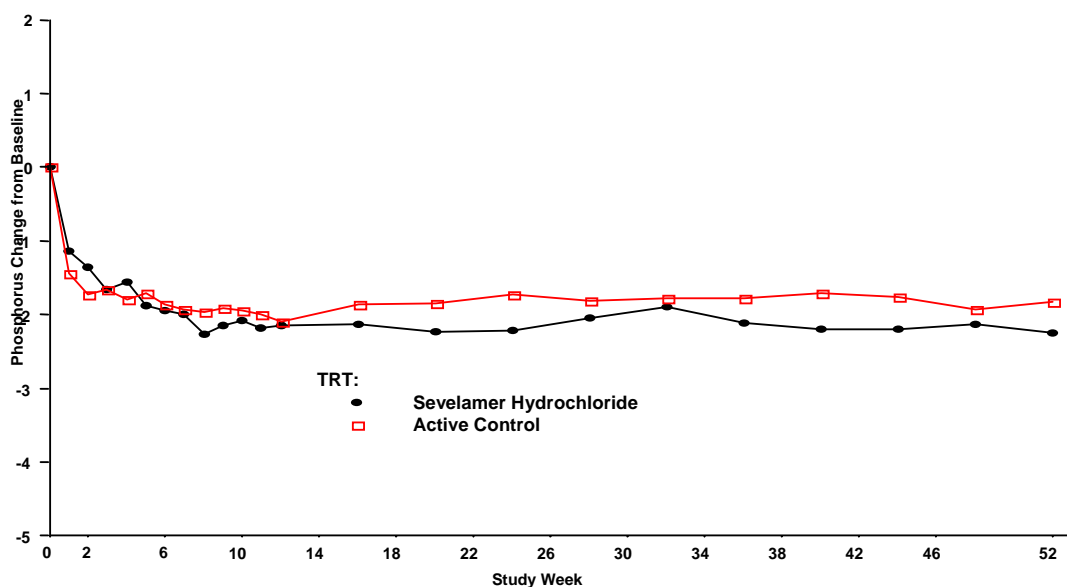
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Change from Baseline at Endpoint	-2.1	-1.8
Ca x Phosphorus Ion Product		
Baseline	70.5	68.4
Change from Baseline at Endpoint	-19.4	-14.2

243 Sixty-one percent of Renagel patients and 73% of the control patients completed the full
 244 52 weeks of treatment.

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

247 **Figure 2. Mean Phosphorus Change from Baseline for Patients who Completed 52**
 248 **Weeks of Treatment**



249
 250
 251 Average daily Renagel dose at the end of treatment was 6.5 g (range of 0.8 to 13 g).

252 **14.3 Active-Control, Parallel Study in Peritoneal Dialysis Patients**

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

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

PROPOSED TEXT OF THE LABELING OF THE DRUG

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

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

268 1 Bottle of 30 ct 800 mg Tablets (NDC 58468-0021-3)

269 1 Bottle of 180 ct 800 mg Tablets (NDC 58468-0021-1)

270 1 Bottle of 360 ct 400 mg Tablets (NDC 58468-0020-1)

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

272 Do not use Renagel® after the expiration date on the bottle.

273 [See USP controlled room temperature]

274 Protect from moisture.

275 **17 PATIENT COUNSELING INFORMATION**

276 **17.1 Dosing Recommendations**

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

280 **17.2 Adverse Events**

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

284 Distributed by:

285 Genzyme Corporation

286 500 Kendall Street

287 Cambridge, MA 02142 USA

genzyme

Renagel[®] Tablets

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288 ¹Registered trademark of Genzyme Corporation.