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*

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

1. INDICATIONS AND USAGE

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

2. DOSAGE AND ADMINISTRATION

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

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

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

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

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

Table 2. Starting Dose for Dialysis Patients Switching From Calcium Acetate to 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

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

3. DOSAGE FORMS AND STRENGTHS

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

4. CONTRAINDICATIONS

Renvela is contraindicated in patients with hypophosphatemia or bowel obstruction.

5. WARNINGS AND PRECAUTIONS

5.1 Use Caution in Patients with Gastrointestinal Disorders

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

5.2 Monitor Serum Chemistries

Bicarbonate and chloride levels should be monitored.

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

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

6. ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

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

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

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

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

6.2 Postmarketing Experience

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

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

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

7. DRUG INTERACTIONS

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

7.1 Ciprofloxacin

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

7.2 Digoxin

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

7.3 Warfarin

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

7.4 Enalapril

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

7.5 Metoprolol

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

7.6 Iron

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

7.7 Other Concomitant Drug Therapy

There are no empirical data on avoiding drug interactions between Renvela and most concomitant drugs. However, 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. Patients taking anti-arrhythmic medications for the control of arrhythmias and anti-seizure medications for the control of seizure disorders were excluded from the clinical trials. Special precautions should be taken when prescribing Renvela to patients also taking these medications.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

8.2 Labor and Delivery

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

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

10. OVERDOSAGE

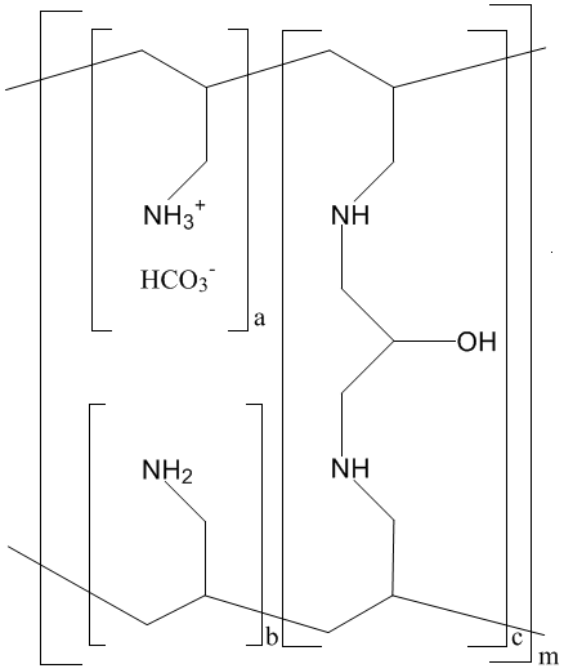
Sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, has been given to normal healthy volunteers in doses of up to 14 grams per day for eight days with no adverse effects. In CKD patients on dialysis, the maximum dose studied was 14 grams of sevelamer carbonate and 13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

11. DESCRIPTION

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

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

Chemical Structure of Sevelamer Carbonate



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

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

12. CLINICAL PHARMACOLOGY

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

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

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

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

12.3 Pharmacokinetics

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

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

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

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

14. CLINICAL STUDIES

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

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

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

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

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

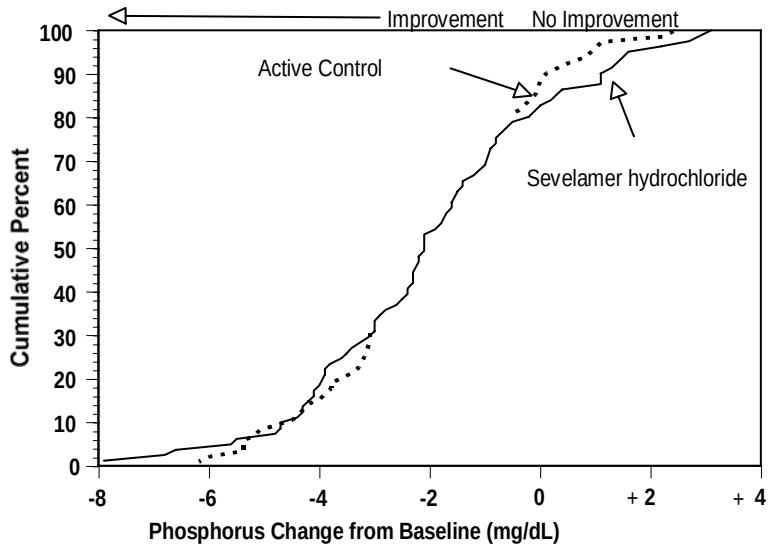
Eighty-four CKD patients on hemodialysis who were hyperphosphatemic (serum phosphorus > 6.0 mg/dL) following a two-week phosphate binder washout period were randomized in a crossover design to receive in random order sevelamer hydrochloride and active comparator for eight weeks each. Treatment periods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

Table 3.
Mean Serum Phosphorus (mg/dL) at Baseline and Endpoint

	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)

*p <0.0001, within treatment group comparison

Figure 1: Cumulative percent 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.



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

14.3 Sevelamer Hydrochloride versus Active-Control in Hemodialysis Patients

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

Table 4:
Mean Serum Phosphorus (mg/dL) and Ion Product at Baseline and Change from Baseline to End of Treatment

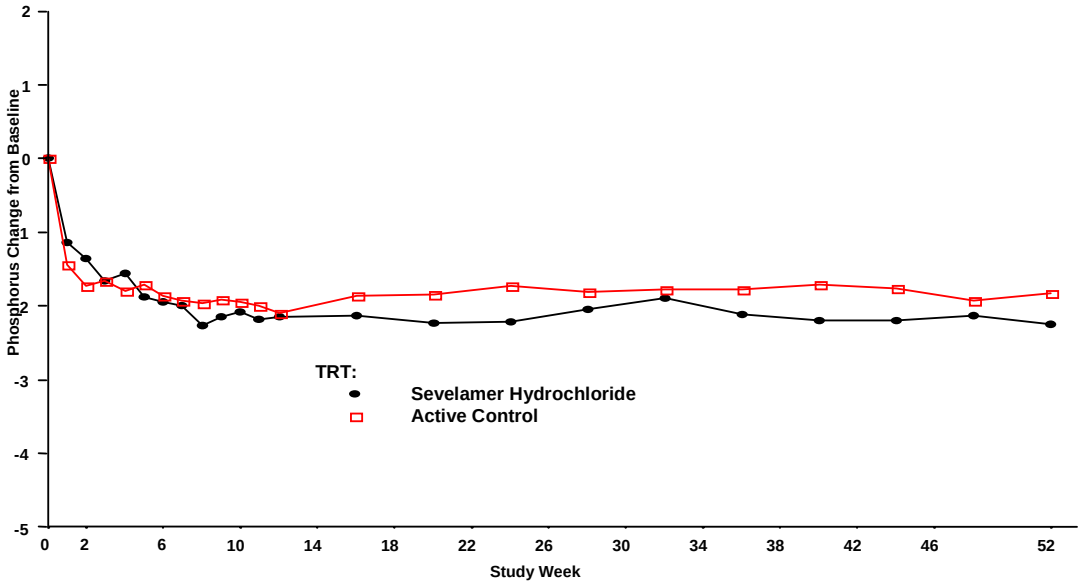
	Sevelamer HCl (N=94)	Active Control (N=98)

	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

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

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

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



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

14.4 Sevelamer Hydrochloride versus Active Control in Peritoneal Dialysis Patients

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

16. HOW SUPPLIED/STORAGE AND HANDLING

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

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

Storage Store at 25°C (77°F): excursions permitted to 15-30°C (59-86°F).
[See USP controlled room temperature]
Protect from moisture.

Shelf life is 24 months.

17. PATIENT COUNSELING INFORMATION

17.1 Dosing Recommendations

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

17.2 Adverse Reactions

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

Distributed by:

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