Renvela
Sevelamer carbonate

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

INDICATIONS AND USAGE
- Renvela is indicated for the control of hyperphosphataemia in adult patients receiving hemodialysis or peritoneal dialysis.

  Renvela is also indicated for the control of hyperphosphataemia in adult patients with chronic kidney disease not on dialysis with serum phosphorus ≥ 1.78 mmol/l.

  Renvela should be used within the context of a multiple therapeutic approach, which could include calcium supplement, 1,25-dihydroxy Vitamin D3 or one of its analogues to control the development of renal bone disease.

DOSAGE AND ADMINISTRATION
- Starting dose is one or 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)
- In patients with hypersensitivity to the active substance or to any of the excipients. (4)

WARNINGS AND PRECAUTIONS
- Serious cases of dysphagia, bowel obstruction, and perforation have been associated with sevelamer use, some requiring hospitalization and surgery. (5.1)

ADVERSE REACTIONS
- The most frequently occurring adverse reactions in a short term study with sevelamer carbonate tablets (8-week cross-over) study were: nausea (3%) and vomiting (3%) . 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)

DRUG INTERACTIONS
- When clinically significant drug interactions are expected, consider separation of the timing of administration and/or monitor clinical responses or blood levels of the concomitant medication. (7)
- Sevelamer did not alter the pharmacokinetics of digoxin, enalapril, iron, metoprolol, and warfarin. (7)
- Sevelamer has demonstrated interaction with ciprofloxacin and mycophenolate mofetil, and therefore these drugs should be dosed separately from Renvela. (7)

See 17 for PATIENT COUNSELING INFORMATION

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1. INDICATIONS AND USAGE

Renvela is indicated for the control of hyperphosphataemia in adult patients receiving hemodialysis or peritoneal dialysis.

Renvela is also indicated for the control of hyperphosphataemia in adult patients with chronic kidney disease not on dialysis with serum phosphorus ≥ 1.78 mmol/l.

Renvela should be used within the context of a multiple therapeutic approach, which could include calcium supplement, 1,25-dihydroxy Vitamin D3 or one of its analogues to control the development of renal bone disease.

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.

Renvela should be given three times a day with meals.

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 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 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.
Renvela is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients.

5. WARNINGS AND PRECAUTIONS

5.1 Gastrointestinal Adverse Events

Cases of dysphagia and esophageal tablet retention have been reported in association with use of the tablet formulation of sevelamer, some requiring hospitalization and intervention.

Cases of bowel obstruction and perforation have also been reported with sevelamer use.

Patients with dysphagia, swallowing disorders, severe gastrointestinal (GI) motility disorders including severe constipation, or major GI tract surgery were not included in the Renvela clinical studies. Use with 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.
It is recommended that CKD patients not on dialysis are given Vitamin D supplements (approximately 400 IU of native vitamin D daily) which can be part of a multivitamin preparation to be taken apart from their dose of Renvela. In patients undergoing peritoneal dialysis, additional monitoring of fat-soluble vitamins and folic acid is recommended, since vitamin A, D, E, and K levels were not measured in a clinical study in these patients.

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 cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of sevelamer (as either carbonate and hydrochloride salts) has been investigated in numerous clinical trials involving a total of 969 hemodialysis patients with treatment duration of 4 to 50 weeks (724 patients treated with sevelamer hydrochloride and 245 with sevelamer carbonate), 97 peritoneal dialysis patients with treatment duration of 12 weeks (all treated with sevelamer hydrochloride) and 128 patients with CKD not on dialysis with treatment duration of 8 to 12 weeks (79 patients treated with sevelamer hydrochloride and 49 with sevelamer carbonate).

The most frequently occurring (≥ 5% of patients) adverse reactions were all in the gastrointestinal disorders system organ class. Most of these adverse reactions were mild to moderate in intensity.

Adverse reactions are listed by frequency in the table below. The reporting rate is classified as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from available data).

Very common: Nausea, vomiting, upper abdominal pain, constipation
Common: Diarrhea, dyspepsia, flatulence, abdominal pain
Not known: Pruritus, rash, intestinal obstruction, ileus/subileus, and intestinal perforation

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

The following adverse reactions have been identified during post-approval use of sevelamer hydrochloride, which has the same active moiety as sevelamer carbonate: pruritus, 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.

During post-marketing experience, hypersensitivity has been reported in patients receiving Renvela.

7. DRUG INTERACTIONS

There are no empirical data on avoiding drug interactions between Renvela and most concomitant oral drugs. For oral medication where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy (e.g., cyclosporine, tacrolimus, levothyroxine), consider separation of the timing of the administration of the two drugs [see Clinical Pharmacology (12.3)]. The duration of separation depends upon the absorption characteristics of the medication concomitantly administered, such as the time to reach peak systemic levels and whether the drug is an immediate release or an extended release product. Where possible consider monitoring clinical responses and/or blood levels of concomitant drugs that have a narrow therapeutic range.

Table 3. Sevelamer Drug Interactions

Oral drugs for which sevelamer did not alter the pharmacokinetics when administered concomitantly	
Digoxin Enalapril Iron Metoprolol Warfarin	
Oral drugs that have demonstrated interaction with sevelamer and are to be dosed separately from Renvela	
	Dosing Recommendations
Ciprofloxacin	Take at least 2 hours before or 6 hours after sevelamer
Mycophenolate mofetil	Take at least 2 hours before sevelamer

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

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 at a dose approximately equal to or higher than the maximum clinical trial dose of 13 g on a body surface area basis. In pregnant rabbits given oral doses of sevelamer hydrochloride by gavage during organogenesis, an increase of early resorptions occurred at dose approximately 1.5 times the maximum clinical trial dose on a body surface area basis. [See NONCLINICAL TOXICOLOGY (13.2)]

8.2 Lactation

It is unknown whether sevelamer is excreted in human breast milk.
The non-absorbed nature of sevelamer indicates that excretion of sevelamer in breast milk is unlikely. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Renvela should be made taking into account the benefit of breast-feeding to the child and the benefit of Renvela therapy to the woman.

8.3 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.

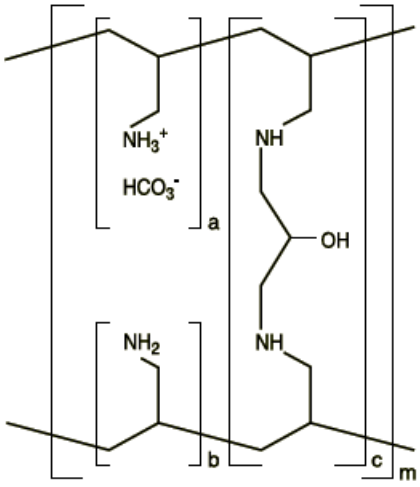
8.5 Geriatric Use
Clinical studies of Renvela did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In 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 in Figure 1.

Figure 1. 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 gastrointestinal tract and decreasing absorption, sevelamer carbonate lowers the phosphate concentration in the serum (serum phosphorus).

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.

Drug Interactions

In vivo

Sevelamer carbonate has been studied in human drug-drug interaction studies (9.6 grams once daily with a meal) with warfarin and digoxin. Sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, has been studied in human drug-drug interaction studies (2.4 - 2.8 grams single dose or three times daily with meals or two times daily without meals) with ciprofloxacin, digoxin, enalapril, iron, metoprolol, mycophenolate mofetil and warfarin.

Co-administered single dose of 2.8 grams of sevelamer hydrochloride in fasted state decreased the bioavailability of ciprofloxacin by approximately 50% in healthy subjects.

Concomitant administration of sevelamer and mycophenolate mofetil in adult and pediatric patients decreased the mean MPA C_{max} and $AUC_{0\text{-}12h}$ by 36% and 26% respectively.

Sevelamer carbonate or sevelamer hydrochloride did not alter the pharmacokinetics of a single dose of enalapril, digoxin, iron, metoprolol and warfarin when co-administered.

During postmarketing experience, cases of increased thyroid stimulating hormone (TSH) levels have been reported in patients co-administered sevelamer hydrochloride and levothyroxine. Reduction in concentrations of cyclosporine and tacrolimus leading to dose increases has also been reported in transplant patients when co-administered with sevelamer hydrochloride without any clinical consequences (for example, graft rejection). The possibility of an interaction cannot be excluded with these drugs.

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).

13.2 Developmental Toxicity

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 approximately equal to or higher than the maximum clinical dose of 13 g on a body surface area basis). 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 1.5 times 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 three clinical trials 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 studies include one double-blind, active-controlled, cross-over study with two 8-week treatment periods using sevelamer carbonate tablets (N=79), one open-label, active-controlled, cross-over study with two 4-week treatment periods using sevelamer carbonate powder (N=31) and one randomized, parallel, open-label study using sevelamer carbonate powder (N=144) dosed once daily or sevelamer hydrochloride tablets (N=73) dosed three times daily for 24 weeks. 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 crossover period was determined based on the sevelamer hydrochloride dose during the run-in period on

a gram per gram basis. The phosphorus levels at the end of each of the two cross-over periods were similar. Average actual daily dose was 6 g/day divided among meals for both treatments. A portion of the patients who completed the cross-over portion of the study were entered into a two-week washout period. During the two-week washout period, patients were instructed not to take any phosphate binders; forty (40) patients completed the washout period and 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 cross-over design to receive in random order sevelamer hydrochloride and active-control 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 phosphorus control. Both treatments significantly decreased mean serum phosphorus by about 2 mg/dL. (Table 4)

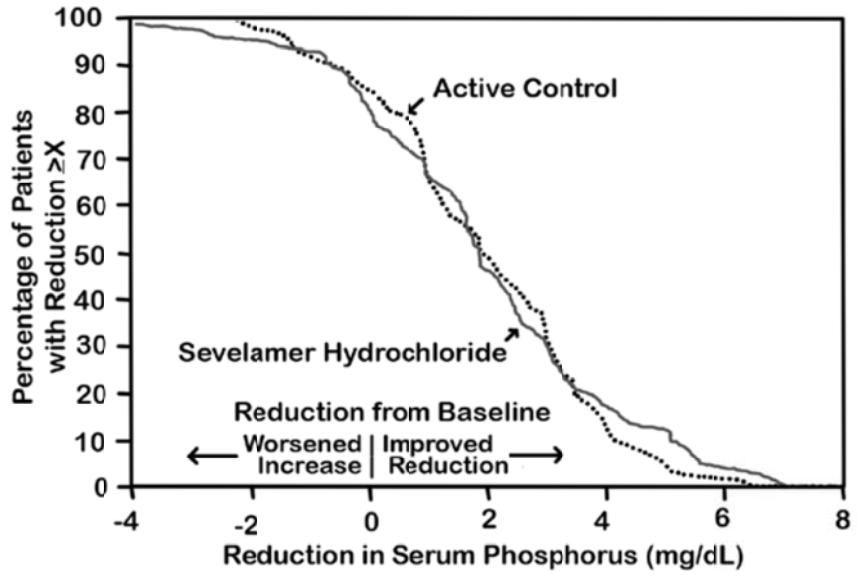
Table 4. Mean Serum Phosphorus (mg/dL) at Baseline and Endpoint

	Sevelamer Hydrochloride (N = 81)	**Active Control (N = 83)**
Baseline at End of Washout	8.4	8.0
Endpoint	6.4	5.9
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

The distribution of responses is shown in Figure 2. The distributions are similar for sevelamer hydrochloride and active control. The median response is a reduction of about 2 mg/dL in both groups. About 50% of subjects have reductions between 1 and 3 mg/dL.

Figure 2. Percentage of patients (Y-axis) attaining a phosphorus reduction from baseline (mg/dL) at least as great as the value of the X-axis.



Average daily sevelamer hydrochloride dose at the end of treatment was 4.9 g (range from 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 active-control both significantly decreased mean serum phosphorus. (Table 5)

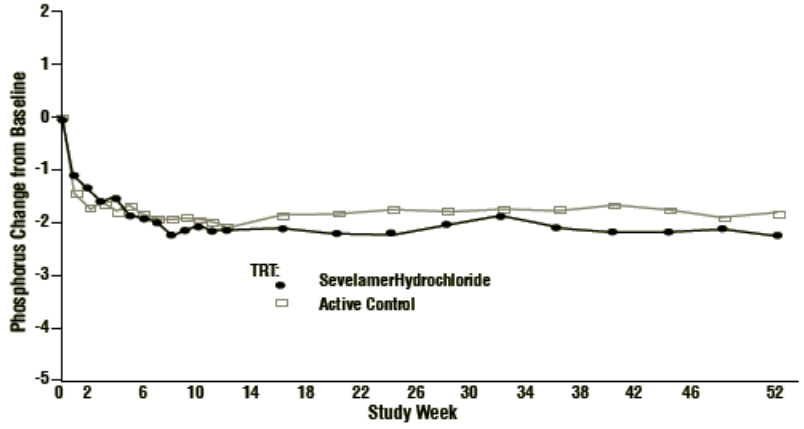
Table 5. Mean Serum Phosphorus (mg/dL) and Ion Product at Baseline and Change from Baseline to End of Treatment

	Sevelamer HCl (N = 94)	**Active Control (N = 99)**
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 hydrochloride patients and 73% of the control patients completed the full 52 weeks of treatment.

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

Figure 3. 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 sevelamer hydrochloride (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 group 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.

14.5 An Open Label, Dose Titration Study of Sevelamer Carbonate Tablets Dosed Three Times A Day In Hyperphosphatemic Chronic Kidney Disease Patients Not On Dialysis

An open-label, single-arm, dose titration study was conducted with sevelamer carbonate tablets in hyperphosphatemic CKD patients not on dialysis. The study included a washout period for those on binder, an 8-week treatment period followed by a post-treatment washout period for all patients. All patients were supplemented with a daily dose of 400 IU of native vitamin D to be taken separately from the dose of sevelamer carbonate. Sevelamer carbonate tablets were dosed three times per day and mean serum phosphorus level decreased from 2.0 mmol/L (6.2 mg/dL) at baseline to 1.6 mmol/L (4.8 mg/dL) at the end of treatment. The decrease in serum phosphorus level was statistically significant [mean 0.5 mmol/L (1.4 mg/dL), $p<0.001$]. During the post-treatment washout period, there was a statistically significant increase in mean serum phosphorus levels of 0.6 mmol/L (1.7 mg/dL) ($p<0.001$) confirming the efficacy of sevelamer carbonate in hyperphosphatemic CKD patients not on dialysis.

15. 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 available as
1 Bottle of 30 ct 800 mg Tablets
1 Bottle of 180 ct 800 mg Tablets
1 Bottle of 270 ct 800 mg Tablets

Not all pack sizes are marketed.

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

16. PATIENT COUNSELING INFORMATION

16.1 Dosing

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

For patients using an oral medication where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy, advise the patient to take the oral medication at least one hour before or three hours after Renvela.

Blood levels of the oral medication should be monitored, if applicable, to determine if there is a significant interaction between the oral medication and Renvela.

16.2 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.

Product Owner

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