1. NAME OF THE MEDICIAL PRODUCT

1.1 Product Name: Renvela®

1.2 Strength: 800 mg (0.8 g)

1.3 Pharmaceutical Dosage Form: Film-coated tablet, Powder for oral suspension

2. QUALITATIVE AND QUALITATIVE COMPOSITION

Each tablet contains 800 mg of Sevelamer Carbonate.

Each sachet contains 0.8 g of Sevelamer Carbonate.

Excipient with known effect

This medicine contains 8.42 mg propylene glycol alginate (E405) in each 0.8 g sachet.

3. PHARMACEUTICAL DOSAGE FORM

Film-coated tablet: White to off-white oval tablet, engraved with "RV800" on one side

Powder for oral suspension: Pale yellow powder packaged in opaque, foil lined, heat sealed, sachets. The sachet consists of a series of arrows indicating where to tear open the sachet.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indication

Renvela® (sevelamer carbonate) is a phosphate binder indicated for the control of serum phosphorus in patients with chronic kidney disease (CKD).

Renvela® is indicated for the control of serum phosphorus in pediatric patients (≥6 years of age and a Body Surface Area (BSA) of ≥0.75 m^2) with chronic kidney disease (CKD).

4.2 Posology and Method of Administration

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

4.2.1 General Dosing Information

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 (0.8 to 1.6 g) 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 Tablet	Renvela® Powder
> 5.5 and < 7.5 mg/dL	1 tablet three times daily with meals	0.8 g three times daily with meals
≥ 7.5	2 tablets three times daily with meals	1.6 g three times daily with meals

Patients Switching From Sevelamer Hydrochloride Tablets. For patients switching from sevelamer hydrochloride tablets to sevelamer carbonate tablets or powder , use the same dose in grams. Further titration may be necessary to achieve desired phosphate levels. The highest daily dose of sevelamer carbonate studied was 14 grams in CKD patients on dialysis.

Switching between Sevelamer Carbonate Tablets and Powder. Use the same dose in grams. Further titration may be necessary to achieve desired phosphorus levels.

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 Patients Switching From Calcium Acetate to Renvela

Calcium Acetate 667 mg (Tablets per meal)	Renvela® 800 mg (Tablets per meal)	Renvela Powder
1 tablet	1 tablet	0.8 g
2 tablets	2 tablets	1.6 g
3 tablets	3 tablets	2.4 g

Dose Titration for All Patients Taking Renvela. Tritate the Renvela dose by 0.8 g three times day with 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.

Pediatric Patients. The recommended starting dose for pediatric patients is based on the patient's Body Surface Area (BSA) category. Renvela must be taken three times per day with meals and /or snacks. If a pediatric patient eats less than 3 meals/snacks per day, Renvela should only be given per meal/snack and not on an empty stomach. For example, if the patient's Screening BSA is ≥0.75 to <1.2 m^2 and the patient eats 2 meals/snacks per day that patient will take 0.8 g BID per meal.

Table 3. Recommended Starting Dosage based on Pediatric Patient's Body Surface Area (BSA) (m^2)

(BSA) (m^2)	Dose per Meal/Snack

≥0.75 to <1.2	0.8 g
>1.2	1.6 g

Special Populations

Children. The safety and efficacy of Renvela has not been established in children below the age of 6 years nor in children with a BSA below 0.75 m^2. Renvela is not recommended for use in children below the age of 6 years.

The safety and effectiveness of sevelamer carbonate in hyperphosphatemic pediatric patients with Chronic Kidney Disease (CKD) was evaluated in a multicenter study with a 2-week, randomized, placebo-controlled, Fixed Dose Period (FDP) followed by a 6-month, single-arm, open-label, Dose Titration Period (DTP). A total of 101 patients (6 to 18 years old) with a BSA range of 0.8 m^2 to 2.4 m^2 were randomized in the study. Forty-nine (49) patients received sevelamer carbonate and 51 patients received placebo during the 2 week FDP; thereafter all patients received sevelamer carbonate for the 26-week Dose Titration Period (DTP). The study met its primary and secondary efficacy endpoints. In pediatric patients with hyperphosphatemia secondary to CKD, sevelamer carbonate significantly reduced serum phosphorus levels compared to placebo during a 2-week FDP. The treatment response was maintained in the paediatric patients who received sevelamer carbonate during the 6-month open-label DTP. No new risks or safety signals were identified with the use of sevelamer carbonate during the study.

4.2.2 Method of Administration

Tablet: Renvela tablets should be swallowed intact and should not be crushed, chewed or broken into pieces prior to administration.

Powder: The entire contents of each 0.8 g sachet should be placed in a cup and mixed thoroughly with the amount of water described in Table 3.

Table 3. Sevelamer Carbonate Powder Preparation Instructions

Renvela Powder Sachet Strength	**Minimum amount of water for dose preparation (either ounces, mL or teaspoon/Tablespoon)**		
	ounces	**mL**	**Tsp/Tbsp**
0.8 g	1	30	6 teaspoon/ 2 Tablespoons

Patients should be instructed to stir the mixture vigorously (it does not dissolve) and drink the entire preparation within 30 minutes and resuspend the preparation right before drinking.

As an alternative to water, the powder may be pre-mixed with a small amount of beverage or food (e.g. 4 ounces/120 ml) and consumed within 30 minutes. Do not heat Renvela powder (e.g., microwave) or add to hot foods or liquids.

PATIENT COUNSELING INFORMATION

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.

Specific Populations

Pediatric Use

The safety and efficacy of Renvela in lowering serum phosphorus levels was studied in patients 6 years of age and older with CKD. In this study, Renvela was apparently less effective in children with a low baseline serum phosphorus, which described children <13 years of age and children not on dialysis. Given its mechanism of action, Renvela is expected to be effective in lowering serum phosphorus levels in pediatric patients with CKD. Most adverse events that were reported as related, or possibly related, to sevelamer carbonate were gastrointestinal in nature. No new risks or safety signals were identified with the use of sevelamer carbonate in the trial.

Renvela has not been studied in pediatric patients below 6 years of age.

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.

4.3 Contraindication

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.

4.4 Special Warning and Precautions for Use

4.4.1 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.

Cases of serious inflammatory disorders of the gastrointestinal tract (with complications including hemorrhage, perforation, ulceration, necrosis, colitis, and colonic/cecal mass) associated with the presence of sevelamer crystals have been reported. Inflammatory disorders may resolve upon Renvela discontinuation. Treatment with Renvela should be re-evaluated in patients who develop severe gastrointestinal symptoms.

4.4.2 Monitor Serum Chemistries

Bicarbonate and chloride levels should be monitored.

4.4.3 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.

4.5 Interaction with Other Medicinal Products and Other Forms of Interactions

Sevelamer carbonate has been studied in two human drug-drug interaction studies. In interaction studies in healthy volunteers, sevelamer carbonate did not affect the bioavailability of either warfarin or digoxin.

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.

4.5.1 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%.

4.5.2 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.

4.5.3 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.

4.5.4 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.

4.5.5 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.

4.5.6 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.

4.5.7 Other Concomitant Drug Therapy

There are no empirical data on avoiding drug interactions between Renvela and most concomitant drugs. During postmarketing experience, very rare cases of increased thyroid stimulating hormone (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. 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.

During postmarketing experience, reduced concentrations of cyclosporin, mycophenolate mofetil and tacrolimus have 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 and close monitoring of blood concentrations of cyclosporin, mycophenolate mofetil and tacrolimus should be considered during the use of any of these agents in combination with sevelamer and after its withdrawal.

Table 4. Sevelamer Drug Interactions

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

4.6 Pregnancy and Lactation

4.6.1 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. Renvela should only be given to pregnant or lactating women if clearly needed and after careful risk/benefit analysis has been conducted for both the mother and fetus or infant.

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 section 5.3 Preclinical Safety Data)*

4.6.2 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 section 5.3 Preclinical Safety Data)*

4.7 Effects on Ability to Drive and Use Machine

No studies on the effects on ability to drive and use machines have been performed.

4.8 Undesirable Effects

4.8.1 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 the fact that it contains the same active ingredient as the hydrochloride salt, the adverse event profiles of the two salts should be similar.

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 treatment with sevelamer hydrochloride and 49 with sevelamer carbonate).

The most frequently occurring (≥ 5% of patients) undesirable effects possibly or probably related to sevelamer were all in the gastrointestinal disorders system organ class. Most of these adverse reactions were mild to moderate in intensity. Data possibly or probably related to sevelamer from these studies are listed by frequency in the table below. The reporting rate is classified as very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Gastrointestinal disorders
Very common : Nausea, vomiting, upper abdominal pain, constipation
Common : Diarrhoea**,** dyspepsia, flatulence, abdominal pain

4.8.2 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: Hypersensitivity, 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.

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.

Cases of serious inflammatory disorders of the gastrointestinal tract (with complications including hemorrhage, perforation, ulceration, necrosis, colitis, and intestinal mass) associated with the presence of sevelamer crystals have been reported.

During post-marketing experience, very rare cases of increased phosphate levels have been reported in patients taking proton pump inhibitors co-administered with sevelamer carbonate.

4.9 Overdose

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.

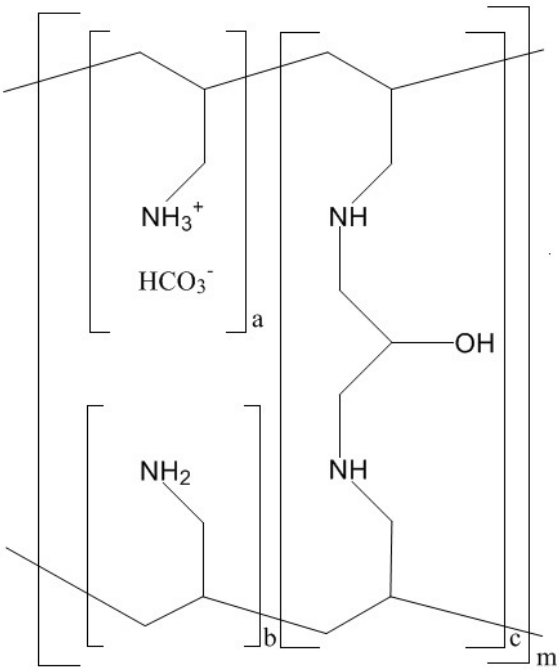
5. PHARMACOLOGICAL PROPERTIES

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 involved in phosphate binding, 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 anhydrous sevelamer carbonate. The inactive ingredients are coating solution (hypromellose and diacetylated monoglycerides), purified water, microcrystalline cellulose, sodium chloride and zinc stearate.

Renvela® Powder: Each sachet of Renvela contains 0.8 g of sevelamer carbonate on an anhydrous basis. The inactive ingredients are natural & artificial citrus cream, propylene glycol algenate, sodium chloride powder, sucralose and ferric oxide (yellow).

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.

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.

5.1 Pharmacodynamic Properties

ATC for sevelamer carbonate is: V03AE02 Treatment of Hyperphosphatemia.

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.

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 in hemodialysis patients 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 open-label, dose titration study of sevelamer carbonate tablets dosed three times a day in hyperphosphatemic chronic kidney disease patients not on. Six studies are described here.

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.

2 Cross-over Study of Sevelamer Carbonate (Renvela®) Powder and Sevelamer Hydrochloride (Renagel®) Tablets

Stage 5 CKD patients on hemodialysis were entered into a four-week sevelamer hydrochloride run-in period and 31 patients received, in random order, sevelamer carbonate powder and sevelamer hydrochloride tablets for four 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 6.0 g/day divided among meals for sevelamer carbonate powder and 6.4 g/day divided among meals for sevelamer hydrochloride tablets.

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

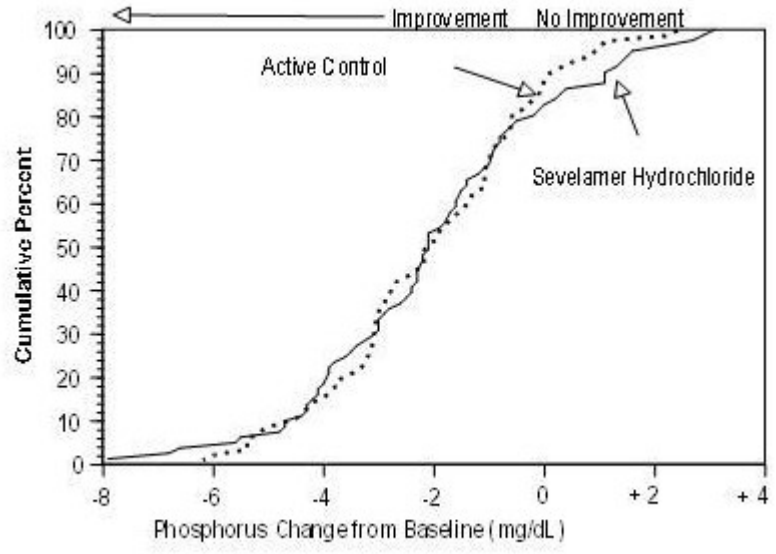
Eighty-four CKD patients on hemodialysis who were hyperphosphatemic (serum phosphorus > 6.0 mg/dL) following a two-week phosphate binder washout period were randomized in a cross-over design to receive in random order sevelamer hydrochloride and active-control for eight weeks each. Treatment periods 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 phosphate control. Both treatments significantly decreased mean serum phosphorus by about 2 mg/dL (Table5).

Table 5. 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
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 2. 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).

4 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 6).

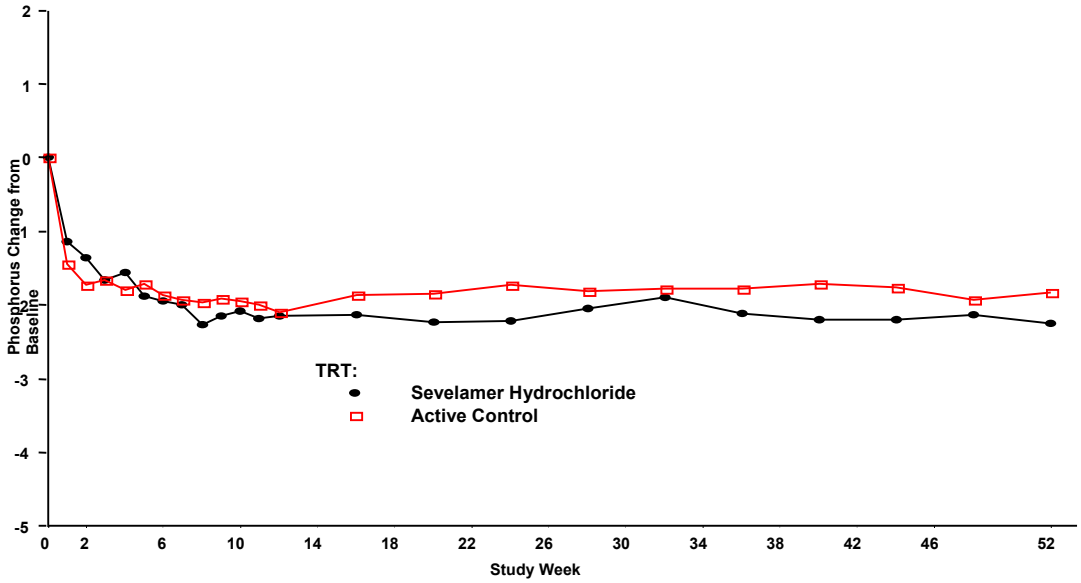
Table 6. Mean Serum Phosphorus (mg/dL) and Ion Product at Baseline and Change from Baseline to End of Treatment

	Sevelamer HCl (N=94)	Active-Control (N=98)
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 the 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).

5 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 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.

6 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.

7 A Clinical Trial With Sevelamer Carbonate In Pediatric Patients.

A clinical trial with sevelamer carbonate was conducted in pediatric patients. This study included a washout period for subjects on a phosphate binder, a 2-week, double-blind, placebo-controlled, Fixed Dose Period (FDP), followed by a 26-week open-label, sevelamer carbonate Dose Titration Period (DTP). In pediatric patients (6 to 18 years old with a BSA range of 0.8 m^2 to 2.4 m^2) with hyperphosphatemia secondary to CKD, sevelamer carbonate significantly reduced serum phosphorus through Week 2 by an LS Mean difference of -0.90 (SE 0.270) mg/dL compared to placebo ($p=0.001$). The study met its primary and secondary efficacy endpoints. A similar treatment response was observed in patients who received

sevelamer carbonate during a 6-month open-label DTP. Sevelamer carbonate significantly reduced serum phosphorus through Week 28/ET: the mean change from baseline to Week 28/ET was -1.18 (SD 2.122) mg/dL [p<0.0001]. Most of AEs reported as related, or possibly related, to sevelamer carbonate were gastrointestinal in nature. No new risks or safety signals were identified with the use of sevelamer carbonate during the study.

5.2 Pharmacokinetic Properties

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.

5.3 Preclinical Safety Data

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).

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 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).

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Tablets: Renvela® 800 mg Tablets are supplied as white to off-white oval tablet, engraved with "RV800" on one side, containing 800 mg of anhydrous sevelamer carbonate, purified water, microcrystalline cellulose, coating solution (hypromellose and diacetylated monoglycerides), sodium chloride, and zinc stearate. Renvela® 800 mg Tablets are packaged in 500 cc bottles of 270 tablets.

1 Bottle of 30 ct 800 mg Tablets

1 Bottle of 180 ct 800 mg Tablets

1 Bottle of 270 ct 800 mg Tablets

Powder: Renvela® for Oral Suspension is packaged in opaque, foil lined, heat sealed, sachets containing 0.8 g of sevelamer carbonate on an anhydrous basis, natural and artificial citrus flavor, propylene glycol alginate, sodium chloride, sucralose, and ferric oxide (yellow).

1 box of 90 sachets. Each sachet contains 0.8 g.

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

Shelf life is 36 months.

6.4 Special Precautions for Storage

Storage Store at temperature not exceeding 30°C (86°F): excursions permitted to 15-30°C (59-86°F).
[See USP controlled room temperature]
Protect from moisture.

6.5 Nature and Contents of Container

Tablet: HDPE bottles with a polypropylene cap and foil induction seal.

Powder: opaque, foil lined, heat sealed, sachets

7. MARKETING AUTHORISATION HOLDER

sanofi-aventis (Thailand) Ltd.

Bangkok, Thailand

8. MARKETING AUTHORISATION NUMBERS

Tablet: 1C 103/54 (N)

Powder: 1C 15059/61 (N)

9. DATE OF AUTHORISATION

Tablet: 28th December 2011 (Approval date from the TFDA)

9th April 2015 (SMP release approval)

Powder: 25th July 2018 (Approval date from the TFDA)

10. DATE OF REVISION OF THE TEXT

Sevelamer Carbonate, CCDS version 8 + Editorial change, 03 April 2024

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