PRODUCT MONOGRAPH

^{Pr}RENVELA®

sevelamer carbonate tablets

800 mg

Phosphate Binder

ATC code: VO3A EO2

sanofi-aventis Canada Inc.
2905 Place Louis-R.-Renaud
Laval, Quebec H7V 0A3

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[Pr]Renvela®

Sevelamer carbonate tablet

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Oral	Tablet / 800 mg	Diacetylated monoglycerides, hypromellose, iron oxide black, isopropyl alcohol, microcrystalline cellulose, propylene glycol, sodium chloride, zinc stearate.

INDICATIONS AND CLINICAL USE

- RENVELA (sevelamer carbonate) is indicated for the control of hyperphosphatemia in patients with end-stage renal disease (ESRD) undergoing dialysis.

CONTRAINDICATIONS

RENVELA (sevelamer carbonate) is contraindicated in the following situations:

- patients with hypophosphatemia
- patients with bowel obstruction
- patients hypersensitive to sevelamer or one of the other ingredients in the product.

WARNINGS AND PRECAUTIONS

SERIOUS WARNINGS AND PRECAUTIONS

Serious cases of dysphagia, bowel obstruction, and perforation have been associated with RENVELA use, some requiring hospitalization and surgery.

General

Patients with renal insufficiency may develop hypocalcemia. As RENVELA does not contain calcium, serum calcium levels should be monitored and elemental calcium should be supplemented whenever considered necessary. In cases of hypocalcemia, patients should be given an evening calcium supplement.

Caution should be exercised to avoid hypophosphatemia, a serum phosphorus of < 0.8 mmol/L (see DOSAGE AND ADMINISTRATION).

Rare serious case reports of difficulty swallowing the RENVELA tablet have been reported. Many of these cases involved patients with contributing co-morbid conditions affecting the ability to swallow including swallowing disorders or oroesophageal abnormalities. Caution should be exercised when RENVELA tablets are used in these patients.

Sevelamer binds to bile acids and, therefore, prevents cholesterol absorption.

The safety and efficacy of RENVELA in patients with renal disease who are not undergoing dialysis has not been established.

Gastrointestinal

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

Cases of bowel obstruction (ileus, subileus) and perforation have also been reported with RENVELA use. Constipation may be a preceding symptom.

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.

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. These patients should be monitored carefully while being treated with RENVELA. RENVELA treatment should be re-evaluated in patients who develop severe constipation or other severe GI symptoms (see ADVERSE REACTIONS).

Special Populations

Pregnant Women: The safety of RENVELA has not been established in pregnant women. In preclinical studies, there was no evidence that sevelamer induced embryolethality, fetotoxicity or teratogenicity at the doses tested (up to 1 g/kg/day in rabbits; up to 4.5 g/kg/day in rats). RENVELA should only be given to pregnant women if the benefits outweigh the risks.

Nursing Women: There have been no adequate, well-controlled studies in nursing women; however since sevelamer is not absorbed, excretion in breast milk is not expected.

Pediatrics: The safety and efficacy of RENVELA has not been established in children below the age of 18 years. RENVELA is not recommended for use in children below the age of 18 years.

Geriatrics: No special considerations are needed for elderly patients.

Monitoring and Laboratory Tests

Bicarbonate and chloride levels should be monitored.

Monitor for reduced vitamins D, E, K 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, and folic acid levels at doses 6-10 times the recommended human dose. In short-term clinical trials, there was no evidence of reduction of 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 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.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

There are limited data on the safety of RENVELA (sevelamer carbonate). However, because 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 patients undergoing hemodialysis with treatment duration of eight weeks each and without a mid-point washout period, the adverse reactions on sevelamer carbonate were similar to those observed on sevelamer hydrochloride.

In long-term studies with sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, the most common adverse events included: vomiting, nausea, diarrhea, dyspepsia, abdominal pain, flatulence and constipation as shown in Table 1.

Based on studies of 8-52 weeks, the most common reasons for withdrawal from sevelamer hydrochloride were gastro-intestinal adverse reactions (3-16%).

In a combined safety database comprised of 483 patients with ESRD undergoing hemodialysis, adverse events reported at an incidence ≥10% are provided in Table 1 below. From this database, adverse events are also presented separately from a single long-term randomized clinical study for sevelamer hydrochloride and calcium. The adverse events presented in the table below are not necessarily attributed to sevelamer hydrochloride treatment. The incidence of these events was not dose related.

Table 1: Adverse Events in Patients with End-Stage Renal Disease undergoing Hemodialysis

	Total AEs reported	52 weeks Study of sevelamer hydrochloride vs. calcium (calcium acetate and calcium carbonate)	
System Organ Class Event	**sevelamer hydrochloride** N = 483 %	**sevelamer hydrochloride** N = 99 %	**calcium** N = 101 %
Gastrointestinal Disorders			
Vomiting	24.4	22.2	21.8
Nausea	25.3	20.2	19.8
Diarrhea	21.1	19.2	22.8
Dyspepsia	15.7	16.2	6.9
Constipation	13.3	8.1	11.9
Infections and Infestations			
Nasopharyngitis	13.9	14.1	7.9
Bronchitis	5.4	11.1	12.9
Upper Respiratory Tract Infection	7.0	5.1	10.9
Musculoskeletal, Connective Tissue and Bone Disorders			
Pain in Limb	13.7	13.1	14.9
Arthralgia	11.4	12.1	17.8
Back Pain	6.0	4.0	17.8
Skin Disorders			
Pruritus	10.4	13.1	9.9
Respiratory, Thoracic and Mediastinal Disorders			
Dyspnea	15.7	10.1	16.8
Cough	11.6	7.1	12.9
Vascular Disorders			
Hypertension	9.3	10.1	5.9
Nervous System Disorders			
Headache	18.4	9.1	15.8
General Disorders and Site Administration Disorders			
Dialysis Access Complication	4.3	6.1	10.9
Pyrexia	8.7	5.1	10.9

In 143 patients with ESRD undergoing peritoneal dialysis with treatment duration of 12 weeks (97 on sevelamer hydrochloride and 46 on a calcium-based product), the safety profile was similar to that reported for hemodialysis patients except for peritonitis which is a known complication in these patients.

Post-Market Adverse Drug Reactions

The following adverse reactions have been identified during post-approval use of sevelamer hydrochloride (which has the same active moiety as RENVELA) although no direct relationship could be established: allergic reactions including angioedema, anaphylaxis (some fatal) and erythema, hypersensitivity vasculitis, pruritus, rash, abdominal pain, fecal impaction, and

uncommon cases of intestinal obstruction, ileus, subileus and intestinal perforation. Cases of diverticulitis were also reported.

DRUG INTERACTIONS

Drug-Drug Interactions

Sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, has been studied in human drug-drug interaction studies. In interaction studies in healthy volunteers, sevelamer hydrochloride had no effect on the bioavailability of a single-dose of digoxin, warfarin, enalapril, metoprolol or iron

However, the bioavailability of ciprofloxacin was decreased by approximately 50% when co-administered with sevelamer hydrochloride in a single dose study. Consequently, sevelamer hydrochloride (and thus sevelamer carbonate) should not be taken simultaneously with ciprofloxacin.

During postmarketing experience, reduced concentrations of cyclosporin, mycophenolate mofetil and tacrolimus have been reported in transplant patients when co-administered with sevelamer hydrochloride. The possibility of an interaction cannot be excluded and close monitoring of blood concentrations of cyclosporin, mycophenolate mofetil and tacrolimus or dosing these medicines apart from RENVELA to prevent GI binding (at least one hour before or three hours after RENVELA) should be considered during the use of any of these agents in combination with RENVELA and after its withdrawal.

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.

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

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 sevelamer carbonate, 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 sevelamer carbonate to patients also taking these medications.

Drug-Food Interactions

There have been no adequate, well-controlled studies regarding the effect of a variety of foods on the intestinal phosphorus binding of sevelamer. In all clinical studies patients were instructed to take sevelamer with meals.

Drug-Herb Interactions

There have been no adequate, well-controlled studies regarding drug-herb interactions.

Drug-Laboratory Interactions

There have been no adequate, well-controlled studies regarding drug-laboratory interactions.

Drug-Lifestyle Interactions

There have been no adequate, well-controlled studies regarding drug-lifestyle interactions.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- RENVELA (sevelamer carbonate) tablets should not be bitten, chewed or broken apart prior to dosing.
- RENVELA should be taken immediately prior to or with meals, since its action is to bind ingested phosphate (see ACTION AND CLINICAL PHARMACOLOGY, Mechanism of Action)
- When administering any other medication where a reduction in the bioavailability of that medication would have a clinically significant effect on safety or efficacy, the physician should consider monitoring blood levels or dosing that medicine apart from RENVELA to prevent GI binding (at least one hour before or three hours after RENVELA).

Recommended Dose and Dosage Adjustment

The recommended dosing to be used when initiating RENVELA in patients not using another phosphate binder are outlined below in Table 2:

Table 2: RENVELA Dosing

Starting Dose	
Initial Serum Phosphorus	**RENVELA**
> 1.8 and < 2.4 mmol/L	3 tablets per day (2.4 grams)
≥ 2.4 mmol/L	6 tablets per day (4.8 grams)

For patients previously on sevelamer hydrochloride, RENVELA should be given on a gram for gram basis with monitoring of serum phosphorus levels to ensure optimal daily doses.

In a study in 84 chronic kidney disease (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 3 gives recommended starting doses of RENVELA based on a patient's current calcium acetate dose.

Table 3. Starting Dose for Dialysis Patients Switching From Calcium Acetate to RENVELA

Calcium Acetate 667 mg (Tablets per meal)	RENVELA 800 mg Tablet (Tablets per meal)
1 tablet	1 tablet
2 tablets	2 tablets
3 tablets	3 tablets

Dose adjustments, when necessary should be done every 1 to 3 weeks by increasing one tablet per meal (3 tablets per day) until the desired serum levels are met.

The total dose should be divided according to the meal portion during the day.

Maintenance

Serum phosphorus should be monitored on a regular basis with the goal of maintaining serum phosphorus levels consistent with current medical standards (see **Dosing Considerations**).

In clinical trials, the average actual daily dose of sevelamer carbonate was approximately 6 g per day. The highest studied daily dose of sevelamer carbonate taken was 14.4 g per day in CKD patients.

Missed Dose

- If a dose is forgotten, it should be skipped. Double dosing is not advisable.

OVERDOSAGE

In CKD patients on dialysis, the maximum dose studied was 14.4 grams of sevelamer carbonate and 13 grams of sevelamer hydrochloride. Sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, has been given to normal healthy volunteers in doses of up to 14.4 grams per day for eight days with no adverse effects. 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.

ACTION AND CLINICAL PHARMACOLOGY

Patients with chronic kidney disease (CKD) retain phosphorus and can develop hyperphosphatemia. High serum phosphorus can precipitate serum calcium resulting in ectopic calcification. When the product serum calcium and phosphorus concentrations (Ca x P) exceeds 4.4 mmol/L, there is an increased risk that ectopic calcification will occur. Hyperphosphatemia plays a role in the development of secondary hyperparathyroidism in renal insufficiency. An increase in parathyroid hormone (PTH) levels is characteristic of patients with chronic renal

failure. Increased levels of PTH can lead to osteitis fibrosa. A decrease in serum phosphorus may decrease serum PTH levels.

Mechanism of Action

Sevelamer carbonate is 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.

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. 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 as well as other substances such as cholesterol.

In vitro equilibrium studies demonstrated that sevelamer hydrochloride tablets and sevelamer carbonate tablets were equivalent in terms of phosphate binding, with and without acid pre-treatment. Kinetic experiments demonstrated that sevelamer carbonate and sevelamer hydrochloride tablets bind phosphate in a similarly rapid manner. Therefore, these *in vitro* studies have shown that sevelamer carbonate and sevelamer hydrochloride tablets are equivalent in their phosphate binding properties.

Sevelamer does not contain calcium and decreases the incidence of hypercalcaemic episodes as compared to patients using calcium based phosphate binders alone. The effects of sevelamer on phosphorus and calcium were proven to be maintained throughout a study with one year follow-up.

Pharmacokinetics

Pharmacokinetic studies have not been carried out with sevelamer carbonate or sevelamer hydrochloride as sevelamer is not absorbed from the GI tract, as confirmed by an absorption study in healthy volunteers. In this study 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.

STORAGE AND STABILITY

Store at controlled room temperature 15°C to 30°C. Protect from moisture and heat.

SPECIAL HANDLING INSTRUCTIONS

None.

DOSAGE FORMS, COMPOSITION AND PACKAGING

RENVELA 800 mg tablets are supplied as white, oval, film-coated, tablets, imprinted with "RENVELA 800", containing 800 mg of sevelamer carbonate on an anhydrous basis, microcrystalline cellulose, sodium chloride, zinc stearate and coating components hypromellose and diacetylated monoglycerides. The tablet printing ink also contains hypromellose in addition to iron oxide black, propylene glycol, isopropyl alcohol.

RENVELA 800 mg tablets are available in bottles of 180 tablets.

RENVELA tablets are packaged in white high-density polyethylene bottles (HDPE), with a child resistant polypropylene cap and an induction seal.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Common name: Sevelamer carbonate (USAN)

Chemical names:

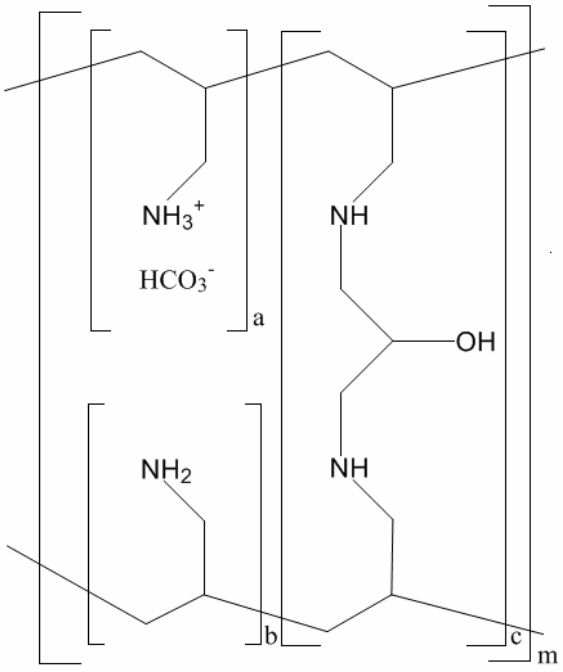
1. poly(allylamine-*co*-*N,N*'-diallyl-1,3-diamino-2-hydroxypropane) carbonate salt (CAS)
2. Oxirane, (chloromethyl)-, polymer with 2-propen-1-amine, carbonate salt (CAS)
3. 2-Propen-1-amine, polymer with (chloromethyl) oxirane, carbonate salt (CAS)
4. Allylamine polymer with 1-chloro-2,3-epoxypropane, carbonate salt (IUPAC)

Molecular formula and molecular mass:

$(C_3H_7N \bullet nH_2CO_3)_{810z}(C_9H_{18}N_2O \bullet nH_2CO_3)_{95z}$ where z = a large number.

Sevelamer carbonate is a highly cross-linked polymer of varying size, and each particle can be considered as one molecule. Since the molecular weight is equal to the weight of the particle itself, the molecular weight distribution of a cross-linked polymer is a function of the distribution of particle sizes.

Structural formula:



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

Physicochemical properties:

Description: Sevelamer carbonate is a cross-linked poly(allylamine carbonate) polymer. The cross-linking agent is epichlorohydrin (1-chloro-2,3-epoxypropane). The cross-linking groups consist of two secondary amine groups derived from the starting material, poly(allylamine hydrochloride) and one molecule of epichlorohydrin giving 2-hydroxypropyl linkers. A portion of the amine is present as the carbonate salt, at 14 – 21% by weight; this is similar to sevelamer hydrochloride where the chloride salt is present at 15 – 20%, by weight.

Physical Form: White to off-white free flowing powder.

Solubilities: Insoluble in all tested solvents.

Crystallinity: Amorphous, granular.

pH Values: 8 – 10.5 (1% aqueous slurry).

Hygroscopicity: Sevelamer carbonate is hygroscopic.

CLINICAL TRIALS

The safety and efficacy of sevelamer to control serum phosphorus in CKD patients on dialysis was mainly determined by the ability of sevelamer hydrochloride to bind phosphorus from food in one double-blind and several open-label clinical trials in hemodialysis and peritoneal dialysis patients.

In a double-blind, randomized, two 8-week period cross-over clinical trial in hemodialysis patients, sevelamer carbonate was shown to be therapeutically equivalent to sevelamer hydrochloride. In this trial, 79 stage 5 CKD patients received, in a random order, sevelamer carbonate 800 mg tablet and sevelamer hydrochloride 800 mg tablets during each 8-week period without an intervening washout phase. The study dose during the cross-over period was based on the sevelamer hydrochloride given during the run-in period. The average actual dose divided among meals during the randomized treatment periods was 6.0 ± 2.8 g/day for both treatment regimens. There was no significant difference in mean serum phosphorus between the two groups during the treatment periods (1.5 ± 0.3 mmol/l during sevelamer carbonate treatment and 1.5±0.3 mmol/l during sevelamer hydrochloride treatment). Following a two-week washout phase after the end of the last period of the cross-over, phosphorus rose significantly to 2.1 ± 0.6 mmol/l.

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

Hemodialysis Patients

Active-Control, Cross-Over Study in Hemodialysis Patients

Eighty-four CKD patients on hemodialysis who were hyperphosphatemic (serum phosphorus > 1.9 mmol/L) following a two-week phosphate binder washout period received sevelamer and active-control for eight weeks each in random order. 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 could be titrated up 1 capsule or tablet per meal (3 per day) 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 0.6 mmol/L (**Table 4**).

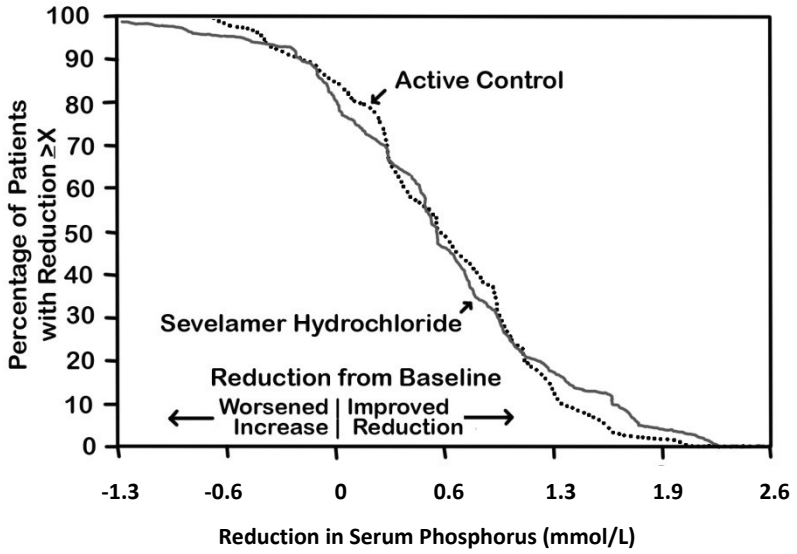
Table 4 Mean Serum Phosphorus (mmol/L) at Baseline and Endpoint

	Sevelamer Hydrochloride (N=81)	Active Control (N=83)
Baseline at End of Washout	2.7	2.6
Endpoint	2.1	1.9
Change from Baseline at Endpoint (95% Confidence Interval)	-0.6* (-0.8, -0.5)	-0.7* (-0.8, -0.5)

*p<0.0001, within treatment group comparison

The distribution of responses is shown in Figure 1. The distributions are similar for sevelamer hydrochloride and active control. The median response is a reduction of about 0.6 mmol/L in both groups. About 50% of subjects have reductions between 0.3 and 1.0 mmol/L.

Figure 1. Percentage of patients (Y-axis) attaining a phosphorus reduction from baseline (mmol/L) 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 of 0.0 to 12.6 g).

Active-Control, Parallel Study in Hemodialysis Patients

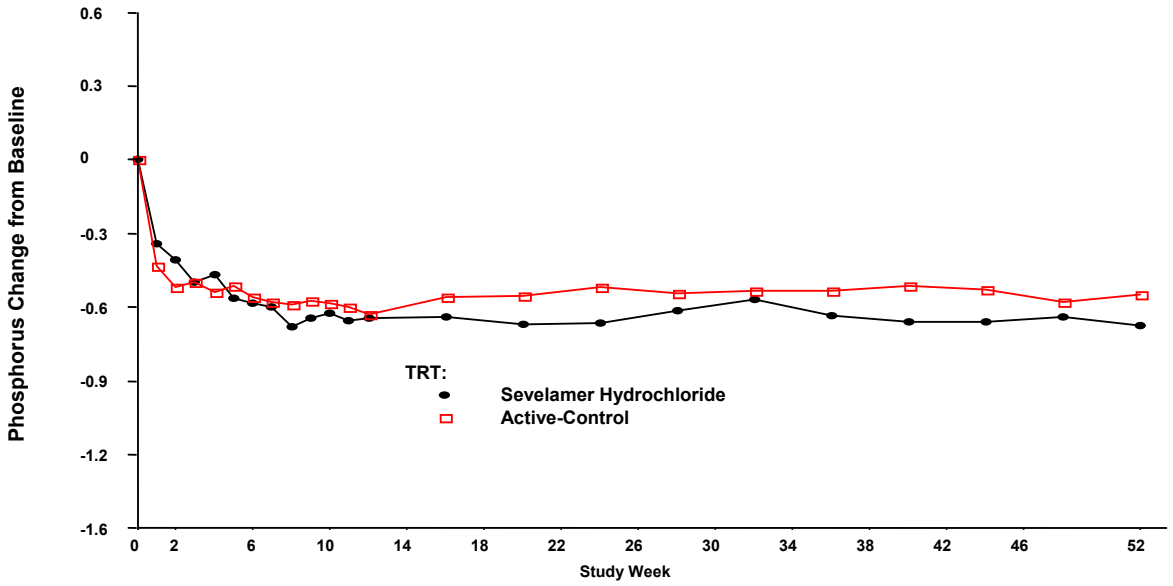
Two hundred CKD patients on hemodialysis who were hyperphosphatemic (serum phosphorus >1.8 mmol/L) following a two-week phosphate binder washout period were randomized to receive sevelamer hydrochloride 800 mg tablets (N=99) or an active-control (N=101). The two treatments produced similar decreases in serum phosphorus. At week 52, using last-observation-carried-forward, sevelamer hydrochloride and active-control both significantly decreased mean serum phosphorus (Table 5).

Table 5. Mean Serum Phosphorus (mmol/L) and Ion at Baseline and Change from Baseline to End of Treatment

	Sevelamer HCl (N=94)	Active-Control (N=98)
Phosphorus Baseline	2.4	2.4
Change from Baseline at Endpoint	-0.7	-0.6
Ca x Phosphorus Ion Product Baseline	5.7	5.5
Change from Baseline at Endpoint	-1.6	-1.1

Sixty-one percent of sevelamer hydrochloride 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).

Active-Control, Parallel Study in Peritoneal Dialysis Patients

One hundred and forty-three patients on peritoneal dialysis who were hyperphosphatemic (serum phosphorus > 1.8 mmol/L) 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).There were statistically significant changes in serum phosphorus ($p<0.001$) for sevelamer hydrochloride (-0.5 mmol/L from baseline of 2.4 mmol/L), similar to the active-control.

DETAILED PHARMACOLOGY

Several *in vitro* assays and animal models were employed to evaluate the activity and efficacy of sevelamer. Administration of sevelamer to normal rats produced 90 and 77% increases in fecal excretion of phosphorus in the two experiments. Calcium carbonate produced a 23% increase in fecal phosphorus excretion compared to a 77% increase produced by sevelamer. Decreased urinary phosphorus, indicating decreased absorption of phosphorus was observed in a dose-dependant manner with sevelamer administration. Animals administered a 0.5% dietary mixture had a 57% decrease in total urinary phosphorus, while animals administered 1, 3 and 9% had 66, 88 and 96% decreases in total urinary phosphorus, respectively. The results from these efficacy studies demonstrate that sevelamer is capable of binding dietary phosphorus in normal animals, preventing GI absorption of phosphorus.

TOXICOLOGY

RENVELA contains sevelamer, a non-absorbed phosphate binding crosslinked polymer, free of metal and calcium. RENVELA (sevelamer carbonate) was developed as a pharmaceutical alternative to sevelamer hydrochloride (RENAGEL®).

Both sevelamer hydrochloride and sevelamer carbonate salt forms are polymeric anion exchange resins with the same polymeric structure. The amines in the polymer exist in a protonated form and bind to negatively charged phosphates. While the counterions differ for the two salts, the polymer itself, the active moiety responsible for binding of phosphate, remains the same. Since in both resins the active moiety responsible for phosphate binding is the same polymer (sevelamer) and the two salts have been shown to be equivalent both in *in vitro* and *in vivo*, the nonclinical data generated using sevelamer hydrochloride are also applicable to sevelamer carbonate.

Carcinogenesis

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 (3 g/kg/day) at a human equivalent dose 2 times the maximum clinical trial dose of 14.4 g/day. Mice received mean dietary doses of 0.8, 3, or 9 g/kg/day. No increased incidence of tumors was observed in mice at a human equivalent dose 3 times the maximum clinical trial dose of 14.4 g/day.

Mutagenesis

A series of genotoxicity studies were performed to assess sevelamer's mutagenic potential. In the Salmonella typhimurium reverse mutation assay, sevelamer produced the same mean number of revertants as the negative control in all strains tested with and without metabolic activation. Sevelamer is considered to be non-mutagenic. In the *in vitro* mammalian cytogenetics test, sevelamer, at 5 mg/mL, was concluded to be weakly positive for the induction of structural

chromosome aberrations and negative for the induction of numerical chromosome aberrations. The weakly positive effects of sevelamer are thought to be due to sevelamer's ability to absorb the culture medium and not the direct action of the test article. Sevelamer was tested in the *in vivo* mouse micronucleus assay to confirm these results. Since sevelamer is non-absorbed, it was injected intraperitoneally to maximize its potential effects. Sevelamer was administered at doses up to 5 g/kg/day for 2 consecutive days. Under the conditions of this study, sevelamer was concluded to be nonclastogenic.

Impairment of Fertility

Developmental and reproductive toxicity studies have been performed with sevelamer to assess teratogenic potential and effects on fertility. In the segment I study, sevelamer had no adverse effect upon male and female fertility or on early embryonic development at the highest dose tested (4.5 g/kg/day). In the segment III pre- and post-natal study, there was no evidence of maternal toxicity at any dose level. There was no effect on reproductive performance during gestation, parturition or lactation and no effect on the survival, physical development, behavior and reproductive performance of the F_1 generation or on the survival and development of the F_2 generation pups at doses tested (≤ 1.0 g/kg/day). In conclusion, no reproductive toxicity has been observed with sevelamer.

Toxicology

To assess nonclinical toxicity, sevelamer was administered orally to Sprague-Dawley rats acutely and for 1, 3, and 6 months at doses up to 10 g/kg/day, and to beagle dogs acutely and for 1, 3, and 12 months at doses up to 2 g/kg/day. In general, sevelamer caused minimal toxicity. In rats, sevelamer produced a dose-dependent decrease in fat-soluble vitamin E and decreased levels of fat-soluble vitamin D and vitamin K (measured by coagulation time) at high doses only. Potentially clinically relevant findings (anemia, focal hemorrhages) due to these decreased serum fat-soluble vitamin levels have only been observed in high-dose (4.5 to 10 g/kg/day) male rats.

In the segment II studies in rats and rabbits, there was no evidence that sevelamer directly induced embryolethality, fetotoxicity, or teratogenicity at the highest doses tested (1.0 g/kg/day in rabbits and 4.5 g/kg/day in rats). In rats, at doses of 1.5 and 4.5 g/kg/day (approximately 8 and 20 times the maximum clinical trial dose of 200 mg/kg/day), sevelamer caused reduced or irregular ossification of fetal bones, probably due to a reduced absorption of fat-soluble vitamin D and/or vitamin K depletion at these high doses.

There are no reported overdoses of sevelamer in patients. Since sevelamer is not absorbed, the risk of systemic toxicity is low.

Studies were conducted with sevelamer carbonate to bridge from the existing toxicology for the hydrochloride salt of sevelamer to the carbonate salt.

To assess nonclinical toxicity, sevelamer hydrochloride and sevelamer carbonate were administered to Sprague Dawley rats and to beagle dogs for four weeks. In rats, two groups received diet mixed with sevelamer carbonate at the dose-level of 1.0 or 4.5 g/kg/day and two other groups received diet mixed with sevelamer hydrochloride at the dose-level of 1.0 or 4.5 g/kg/day. In dogs, treated animals received either sevelamer carbonate or sevelamer

hydrochloride once daily by oral gavage at a dose-level of 0.2 or 1.0 g/kg/day. Other than the reduced serum levels of fat soluble vitamins in rats, no systemic toxicity related to administration of sevelamer carbonate or sevelamer hydrochloride was observed. In addition, these findings were comparable to those seen with similar studies conducted with sevelamer hydrochloride.

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PART III: CONSUMER INFORMATION

[Pr]Renvela®

Sevelamer carbonate tablets

This leaflet is part III of a three-part "Product Monograph" published when RENVELA was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about RENVELA. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

- the control of high phosphorus levels in patients with end stage kidney disease undergoing dialysis (whether hemodialysis or peritoneal dialysis)

What it does:

RENVELA is a phosphate binder that is not absorbed in your body. When taken with meals RENVELA inhibits intestinal absorption of ingested phosphate from food.

When it should not be used:

- in patients with low phosphorus levels
- in patients with bowel obstruction/blockage
- in patients allergic to sevelamer carbonate or one of the other ingredients in the product (See What the nonmedicinal ingredients are).

What the medicinal ingredient is:

Sevelamer carbonate

What the nonmedicinal ingredients are:

Diacetylated monoglycerides, hypromellose, iron oxide black, isopropyl alcohol, microcrystalline cellulose, propylene glycol, sodium chloride, zinc stearate.

What dosage forms it comes in:

800 mg tablets

WARNINGS AND PRECAUTIONS

SERIOUS WARNING AND PRECAUTION

Renvela may cause serious side effects that may require hospitalization and surgery. Tell your doctor or go to the hospital right away if you have difficulty swallowing, bowel obstruction, or bowel perforation.

RENVELA tablets should be swallowed whole and should not be crushed, chewed, or broken into pieces.

BEFORE you use RENVELA talk to your doctor or pharmacist if you:

- have difficulty swallowing (swallowing disorders or problems with your esophagus)
- have an intestinal disorder such as, conditions that slow down the passage of food through the intestine and lead to blockage.
- have had surgery on your intestines.
- have severe or worsening constipation
- have low phosphorus levels in your blood.
- have low calcium levels in your blood.
- are pregnant, plan to become pregnant or are nursing
- have any allergies to this drug or its ingredients or components of the container

INTERACTIONS WITH THIS MEDICATION

RENVELA may affect the way other medicines work. Please tell your doctor or pharmacist what medicine you have recently taken, are taking or intend to take including those available without prescription and herbal remedies. These medicines may need to be taken one hour before or three hours after RENVELA. Remember, RENVELA must always be taken with food.

If you see another doctor or a dentist while you are using RENVELA, you should tell them that you are using RENVELA.

Drugs that may interact with RENVELA include: ciprofloxacin and levothyroxine. Your doctor may order blood tests to more closely monitor the thyroid hormones in your blood if you are taking levothyroxine and RENVELA.

RENVELA may also interact with drugs that are used to prevent the rejection of a transplanted organ, such as cyclosporin, mycophenolate and tacrolimus.

RENVELA may interact with drugs that are used to treat stomach ulcer known as proton pump inhibitors (e.g. pantoprazole, omeprazole).

PROPER USE OF THIS MEDICATION

Tablets should be swallowed intact and should not be crushed, chewed, or broken into pieces prior to administration.

Usual starting dose:

Dosage is individualized. Your doctor will determine your dosage.

RENVELA should be taken immediately prior to or with meals.

The total daily dose should be divided according to meal portions during the day.

Average maintenance dose is approximately 7-8 tablets of 800 mg each day. Always follow your physician's dosage instructions.

Overdose:

In case of an overdose, contact your doctor or regional poison control center immediately.

Missed Dose:
If a dose is forgotten, it should be skipped. Double dosing is not advisable.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Although RENVELA is generally well tolerated, some patients may experience side effects, including: nausea, vomiting, diarrhea, indigestion, constipation, abdominal pain, rash, itch, and flatulence (gas). Tell your doctor if you have new onset or worsening of constipation.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Abdominal pain		✓	
Uncommon	**Dysphagia:** Difficulty swallowing problems with your esophagus	✓		
	Bowel Obstruction (ileus), **Intestinal Blockage, or hole in the intestine:** abdominal discomfort, cramping and gas pains, difficulty passing stools, nausea/vomiting especially after meals, excessive burping; later symptoms include fever and chills			✓
Unknown	**Diverticulitis:** left lower quadrant pain, fever, nausea, diarrhea, or constipation		✓	
	Allergic reactions: rash, swelling of the face or mouth, difficulty breathing.			✓

This is not a complete list of side effects. For any unexpected effects while taking RENVELA, contact your doctor or pharmacist.

HOW TO STORE IT

Store at controlled room temperature 15°C to 30°C. Protect from moisture and heat.

Keep out of reach and sight of children.

Reporting Suspected Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 1908C
    Ottawa, ON K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website www.sanofi.ca, or by calling 1-800-265-7927.

This leaflet was prepared by sanofi-aventis Canada Inc.

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