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## PRODUCT MONOGRAPH

**Pr**RENAGEL<sup>®</sup>

**sevelamer hydrochloride tablets**

800 mg tablets

Phosphate Binder

ATC code: VO3A EO2

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# PrRenagel<sup>®</sup>

## Sevelamer hydrochloride tablets

### PART I: HEALTH PROFESSIONAL INFORMATION

#### SUMMARY PRODUCT INFORMATION

<b>Route of Administration</b>	<b>Dosage Form / Strength</b>	<b>Clinically Relevant Nonmedicinal Ingredients</b>
Oral	Tablet / 800 mg	There are no clinically relevant nonmedicinal ingredients. Nonmedicinal ingredients include: hypromellose; diacetylated monoglyceride; colloidal silicon dioxide; and stearic acid. The tablet imprint contains iron oxide black ink. <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

#### INDICATIONS AND CLINICAL USE

RENAGEL (sevelamer hydrochloride) is indicated for:

§ the control of hyperphosphatemia in patients with end-stage renal disease (ESRD) undergoing dialysis.

#### CONTRAINDICATIONS

RENAGEL (sevelamer hydrochloride) is contraindicated in the following situations:

- patients with hypophosphatemia
- patients with bowel obstruction
- patients hypersensitive to sevelamer hydrochloride or one of the other ingredients in the product (colloidal silicon dioxide, stearic acid).

## WARNINGS AND PRECAUTIONS

### **General**

RENAGEL (sevelamer hydrochloride) tablets should be swallowed intact and should not be crushed, chewed, or broken into pieces.

Patients with renal insufficiency may develop hypocalcemia. As RENAGEL 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. Approximately 1000 mg elemental calcium is recommended.

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

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

### **Gastrointestinal**

The safety and efficacy of RENAGEL in patients with dysphagia, swallowing disorders, severe gastrointestinal (GI) motility disorders including severe constipation, or major GI tract surgery have not been established. Caution should be exercised when RENAGEL is used in patients with these GI disorders.

### **Special Populations**

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

**Nursing Women:** There have been no adequate, well-controlled studies in lactating, or nursing women.

**Pediatrics:** The safety and efficacy of RENAGEL has not been established in pediatric patients. The minimum age of patients treated with RENAGEL in clinical trials was 18 years old.

**Geriatrics:** No special considerations are needed for elderly patients.

### **Monitoring and Laboratory Tests**

Serum phosphorus and serum calcium should be monitored every 1 to 3 weeks until the target phosphorus level is reached. The dose of RENAGEL should be adjusted based on serum phosphorus concentration and titrated to a target serum phosphorus of  $\leq 1.8$  mmol/L.

RENAGEL does not contain calcium or alkali supplementation; serum calcium, bicarbonate, and chloride levels should be monitored.

### **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.*

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

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

System Organ Class Event	Total AEs reported	52 weeks Study of RENAGEL vs. calcium (calcium acetate and calcium carbonate)	
	RENAGEL N = 483 %	RENAGEL N = 99 %	calcium N = 101 %
<b>Gastrointestinal Disorders</b>			
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
<b>Infections and Infestations</b>			
Nasopharyngitis	13.9	14.1	7.9
Bronchitis	5.4	11.1	12.9
Upper Respiratory Tract Infection	7.0	5.1	10.9
<b>Musculoskeletal, Connective Tissue and Bone Disorders</b>			
Pain in Limb	13.7	13.1	14.9
Arthralgia	11.4	12.1	17.8
Back Pain	6.0	4.0	17.8
<b>Skin Disorders</b>			
Pruritus	10.4	13.1	9.9
<b>Respiratory, Thoracic and Mediastinal Disorders</b>			
Dyspnea	15.7	10.1	16.8
Cough	11.6	7.1	12.9
<b>Vascular Disorders</b>			
Hypertension	9.3	10.1	5.9
<b>Nervous System Disorders</b>			
Headache	18.4	9.1	15.8
<b>General Disorders and Site Administration Disorders</b>			
Dialysis Access Complication	4.3	6.1	10.9
Pyrexia	8.7	5.1	10.9

In one hundred and forty three patients with end-stage renal disease undergoing peritoneal dialysis with treatment duration of 12 weeks, adverse events reported at an incidence  $\geq 10\%$  are provided in Table 2 below. The adverse events presented in the table below are not necessarily attributed to RENAGEL treatment. The incidence of these events was not dose related.

**Table 2: Adverse Events in Patients with End-Stage Renal Disease Undergoing Peritoneal Dialysis**

System Organ Class	<b>RENAGEL</b> (N=97)	<b>calcium</b> (N=46)
Event	%	%
<b>Gastrointestinal disorders</b>		
Dyspepsia	17.5	8.7
Vomiting	11.3	4.3
Peritonitis	11.3	4.3

The most frequently occurring serious adverse event with RENAGEL use was peritonitis at 8.2%, compared to 4.3 % with calcium. Patients receiving dialysis are subject to certain risks for infection specific to the dialysis modality. Peritonitis is a known complication in patients receiving peritoneal dialysis (PD). Therefore, patients on PD should be closely monitored to ensure the reliable use of appropriate aseptic technique with the prompt recognition and management of any signs and symptoms associated with peritonitis.

#### **Less common clinical trial adverse events**

The following adverse events have been observed with RENAGEL use with an incidence of  $<10\%$ , but greater than calcium and without attribution to causality, including: abdominal distension, constipation, diarrhea, nausea, chest pain, fatigue, pyrexia, catheter site infection, anorexia, headache, cough and pruritis.

Some patients experienced adverse events related to hypercalcemia in the calcium group but not in the RENAGEL group.

#### **Post-Market Adverse Drug Reactions**

During post-marketing experience with RENAGEL, the following have been reported without attribution to causality: pruritis, rash, abdominal pain and in very rare cases, intestinal obstruction, ileus and intestinal perforation.

## **DRUG INTERACTIONS**

### **Drug-Drug Interactions**

RENAGEL (sevelamer hydrochloride) was studied in human drug-drug interaction studies with digoxin, warfarin, enalapril, metoprolol and iron. RENAGEL had no effect on the bioavailability of these medications. However, in a study of 15 healthy subjects, a co-administered single dose of 7 RENAGEL Capsules (approximately 2.8 g) decreased the bioavailability of ciprofloxacin by approximately 50%. Consequently, RENAGEL should not be taken simultaneously with ciprofloxacin.

During post-marketing experience, very rare cases of increased TSH levels have been reported in patients co-administered RENAGEL and levothyroxine. Closer monitoring of TSH levels is therefore recommended for patients receiving both medications.

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 RENAGEL (at least one hour before or three hours after RENAGEL). Patients taking anti-arrhythmic and anti-seizure medications were excluded from the clinical trials. Special precautions should be taken when prescribing RENAGEL 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 RENAGEL.

### **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

- The tablets should not be bitten, chewed or broken apart prior to dosing.
- RENAGEL (sevelamer hydrochloride) 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 RENAGEL to prevent GI binding (at least one hour before or three hours after RENAGEL).

### Recommended Dose and Dosage Adjustment

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

Starting Dose	
Initial Serum Phosphorus	RENAGEL Tablets 800 mg
> 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)

When switching from calcium-based phosphate binders to RENAGEL, an equivalent starting dose on a mg/weight basis of RENAGEL should be prescribed.

Dosage adjustments, when necessary should be recommended every 1 to 3 weeks by increasing one tablet per meal (3 per day) until the target serum phosphorus levels are met.

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

**Average Maintenance Dose:** Dosage should be adjusted based upon the target serum phosphorus levels. The dose may be increased or decreased by one tablet per meal at two week intervals as necessary. The average final dose in the chronic phase of a 52 week Phase 3 clinical trial designed to lower serum phosphorous to 1.6 mmol/L or less was approximately 7.1 grams, (approximately nine 800 mg tablets per day equivalent to three 800 mg tablets per meal). The maximum average daily RENAGEL dose studied was 13 grams.

### **Missed Dose**

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

### **OVERDOSAGE**

Since RENAGEL (sevelamer hydrochloride) is not absorbed, the risk of systemic toxicity is minimal. RENAGEL has been given to healthy volunteers at doses up to 14 grams per day for 8 days with no adverse effects. The maximum average daily dose of RENAGEL that has been given to hemodialysis patients is 13 grams.

### **ACTION AND CLINICAL PHARMACOLOGY**

Patients with end-stage renal disease (ESRD) 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 bone disease. A decrease in serum phosphorus may decrease serum PTH levels.

### **Mechanism of Action**

RENAGEL (sevelamer hydrochloride) is a nonabsorbed polymer phosphate binder. When taken with meals RENAGEL inhibits intestinal absorption of ingested phosphate.

RENAGEL binds bile acids and therefore lowers LDL serum cholesterol. Since RENAGEL does not contain aluminum or other metals, it does not cause aluminum or other metal intoxication.

### **Pharmacokinetics**

A mass balance study using <sup>14</sup>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.

## **SPECIAL HANDLING INSTRUCTIONS**

None.

## **DOSAGE FORMS, COMPOSITION AND PACKAGING**

RENAGEL (sevelamer hydrochloride) tablets are film-coated compressed tablets containing 800 mg of sevelamer hydrochloride. RENAGEL contains the following excipients: colloidal silicon dioxide and stearic acid. The RENAGEL tablet coating contains hypromellose and diacetylated monoglyceride. The printing ink contains iron oxide black (E172), propylene glycol, isopropyl alcohol and hypromellose (hydroxypropyl methylcellulose).

RENAGEL 800 mg Tablets are supplied as oval, film-coated tablets, imprinted with “RENAGEL 800,” on the crown, single side.

RENAGEL 800 mg Tablets are available in bottles of 180 tablets.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

Proper name: Sevelamer hydrochloride (USAN)

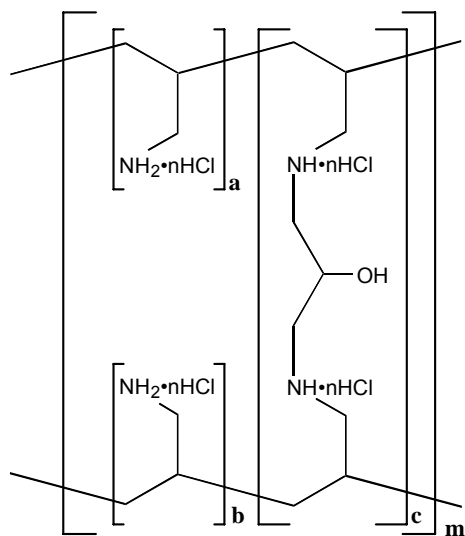
Chemical name:

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

Molecular formula and molecular mass:

$(C_3H_7N \cdot nHCl)_{812z}(C_9H_{18}N_2O \cdot nHCl)_{94z}$  where  $z =$  a large number. The equivalent molecular weight, which corresponds to 1.0 allylamine unit, 0.094 hydroxypropyl units and 0.40 HCl, is 77.1 grams/mole.

Structural formula:



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

Physicochemical properties:

Description: Sevelamer hydrochloride is a cross linked poly(allylamine hydrochloride) polymer. The cross linking agent is epichlorohydrin (1-chloro,2,3-epoxypropane). A portion of the amine is present as the hydrochloride salt; the finished polymer is 40% amine hydrochloride and 60% free amine.

Physical Form: White to off-white powder.

Melting Point: Indistinct melting point. Starts to decompose at >180°C.

Solubilities: Insoluble in all tested aqueous and organic solvents.

Crystallinity: Amorphous with no crystalline structure.

pH Values: A 1% slurry in 0.01 KCl results in a pH between 7.5-8.5.

Hygroscopicity: Sevelamer hydrochloride is hygroscopic.

## CLINICAL TRIALS

### Hemodialysis Patients

The effect of RENAGEL (sevelamer hydrochloride) was investigated in three Phase 2 studies with treatment duration ranging from 2-12 weeks and two Phase 3 studies with treatment duration of 8 weeks in patients (age 18-86 years ) with end-stage renal disease on hemodialysis for 1-20 years. Four of the five studies were open-label dose-titration studies. A total of four hundred and eight patients on hemodialysis who were hyperphosphatemic (serum phosphorus >1.76 mmol/L) following a two-week phosphate binder washout period received RENAGEL. Patients were taken off their current calcium phosphate binder for 2 weeks (first washout period), followed by a treatment period with RENAGEL, and then a final 2 week washout period. Eighty patients also received calcium in a cross-over fashion while thirty-six received RENAGEL in combination with calcium, two received only calcium in the crossover study, and 12 received placebo.

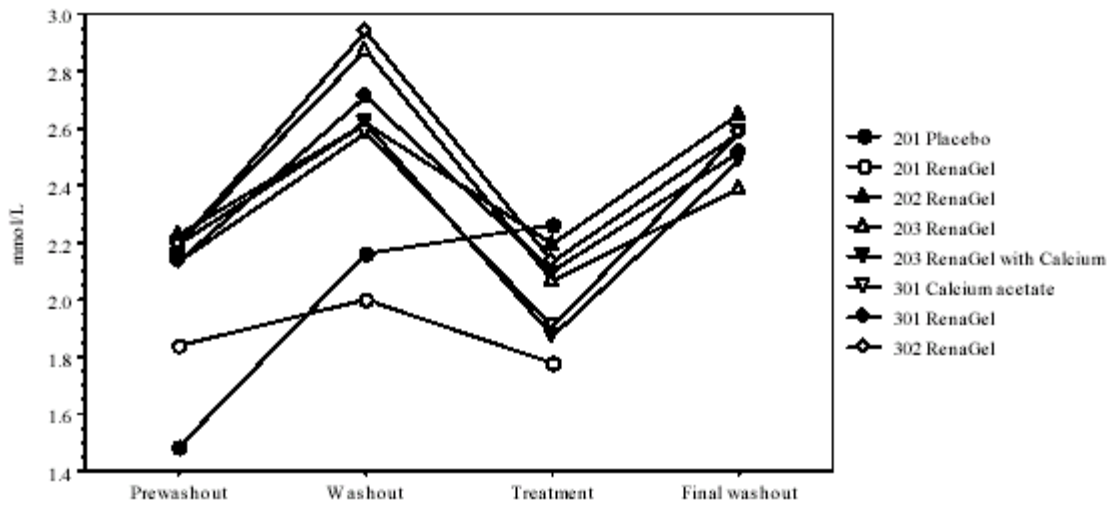
In Study 203, RENAGEL was compared to RENAGEL + evening calcium carbonate and in Study 301, RENAGEL effect was compared to calcium acetate. The results of all studies consistently show the phosphate binding effect of RENAGEL resulting in lowering of serum phosphorus levels. There were statistically significant changes in serum phosphorus ( $p < 0.001$ ) from baseline for RENAGEL (ranging from -0.23 mmol/L to - 0.81 mmol/L). The starting doses varied from 1320 to 2640 mg per day and the average daily dose at the end treatment varied between 4200 and 6400 mg (anhydrous).

(Note: The numbers in the legends to the figures refer to protocol numbers.)

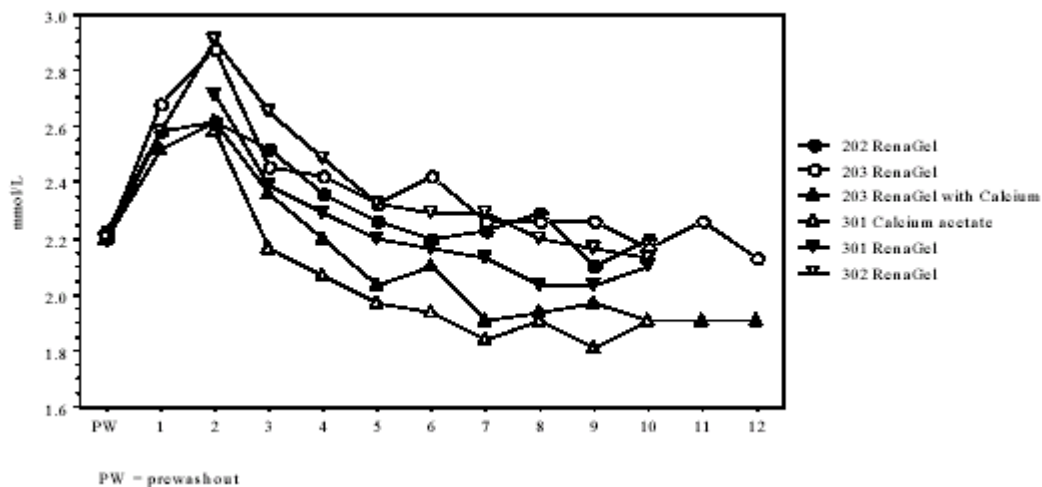
**a. Phosphorus**

The primary end points, serum phosphorus and change in serum phosphorus were statistically and clinically significantly improved with RENAGEL treatment as illustrated in Figures 1 and 2 below.

**Figure 1: Mean Serum Phosphorus Concentrations (mmol/L) Over Time**



**Figure 2: Changes in Serum Phosphorus on a Weekly Basis in Patient Studies**

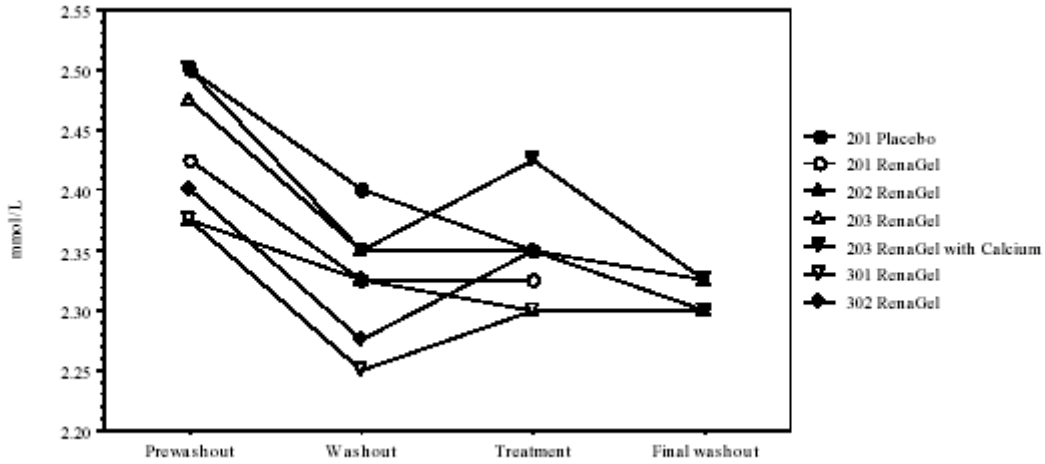


RENAGEL has been shown to be as effective as calcium carbonate and calcium acetate phosphate binders. The phosphate lowering effect was maintained in (compliant) patients over 44 weeks of treatment.

**b. Calcium**

RENAGEL did not affect serum calcium levels as seen in Figure 3.

**Figure 3: Mean Serum Calcium Concentrations (mmol/L) Over Time**

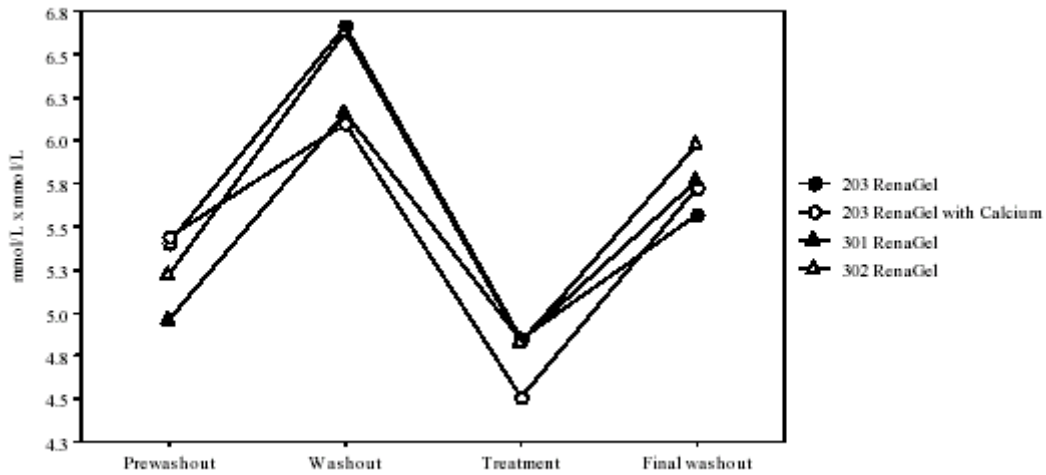


Withdrawal from calcium phosphate binder and subsequent treatment of the same patients with RENAGEL has lowered the incidence of hypercalcemic events (serum Ca > 2.75 mmol/L) from 22% to 5%.

### c. Calcium x Phosphorus Product

With RENAGEL treatment, mean calcium x phosphorus product declined to levels below prewashout levels. With cessation of RENAGEL treatment, calcium x phosphorus products again rose as illustrated in Figure 4.

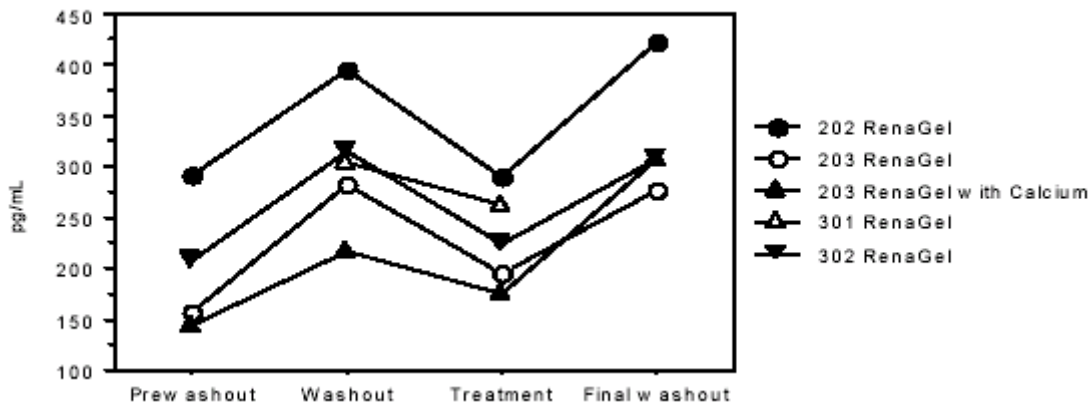
**Figure 4: Mean Serum Calcium x Phosphorus Product (mmol/L x mmol/L) Over Time**



### d. Intact Parathyroid Hormone (iPTH)

During the first washout period, levels of serum phosphorus rose and serum calcium declined as patients were taken off their treatment with calcium based phosphate binders. High serum phosphorus and low serum calcium are stimuli for secretion of iPTH. With RENAGEL treatment, serum iPTH again declined as illustrated in Figure 5.

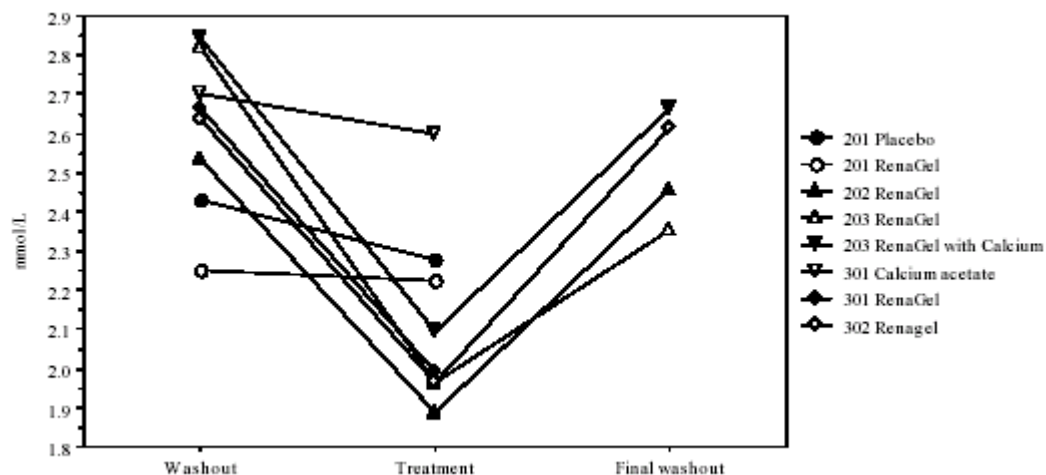
**Figure 5: Median Intact Parathyroid Hormone Concentration (pg/mL)**



### e. Lipid Lowering Effect of RENAGEL

LDL cholesterol fell with RENAGEL treatment but did not change with placebo or calcium acetate. LDL cholesterol percentage change ranged from -15% to -31%. The changes in LDL cholesterol are summarized in Figure 6. Triglyceride and high-lipoprotein cholesterol (HDL-C) did not change significantly. The studies carried out were not designed to study effects on lipids. In addition, it has never been demonstrated that lowering total and LDL cholesterol lead to clinical benefits in patients with end-stage renal disease, regardless if the patients were hypercholesterolemic or dyslipidemic.

**Figure 6: Mean Serum LDL Cholesterol Concentration (mmol/L)**



### Peritoneal Dialysis Patients

One hundred and forty three patients on peritoneal dialysis who were hyperphosphatemic (serum phosphorus >1.76 mmol/L) following a two-week phosphate binder washout period were randomized in a single study to receive RENAGEL 800 mg tablets (N=97) or calcium acetate (N=46). There were statistically significant changes in serum phosphorus ( $p < 0.001$ ) from baseline for both the RENAGEL (-0.52 mmol/L from 2.40 mmol/L) and calcium acetate (-0.58 mmol/L from 2.34 mmol/L). The magnitude of the reduction in serum phosphate over time was similar to that seen in the hemodialysis population.

Average daily consumption at the end of treatment was 5.9 g for RENAGEL (range 0.8 to 14.3 g) and 4.3 g for calcium acetate (range 1.7 to 9.0 g). During calcium acetate treatment, 18% of patients has a serum calcium corrected for albumin  $\geq 11.0$  mg/dL at the end of the study versus 2% for RENAGEL ( $p=0.001$ ).

Reductions in total and LDL cholesterol were seen with RENAGEL, but not with calcium, in a manner consistent with that of hemodialysis patients.

## Long-Term Clinical Trials in Hemodialysis Patients

Hemodialysis patients were treated in two long-term studies, one an open-label extended study of 44 weeks and the other a randomized open-label comparison with calcium-based phosphate binders in 200 patients. ESRD patients on hemodialysis who were hyperphosphatemic (serum phosphorous 1.8 mmol/L) following a two-week phosphate binder washout period were randomized to receive RENAGEL 800 mg tablets (N=99) or calcium, either calcium acetate (N=54) or calcium carbonate (N=47). The daily doses administered were adjusted according to serum levels of phosphorus and calcium. Calcium acetate and calcium carbonate produced comparable decreases in serum phosphorous. At week 52, both RENAGEL and calcium significantly decreased mean serum phosphorous by over 0.65 mmol/L.

In the 44-week, open label extended study, there were no significant change in the levels of lipid soluble vitamins A, D, E (but not that of folic acid).

## 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 gastrointestinal absorption of phosphorus.

## TOXICOLOGY

### Carcinogenesis

Overall, carcinogenicity studies in rats and mice provide no evidence for potential carcinogenesis of sevelamer. In mice, histological exams indicated an increase of lymphoma in the high dose females (50,000 ppm dietary level, 80 to 100 times the projected human dose) when compared to one control group, but not the other control group. The toxicological significance was considered equivocal. In male rats, treatment at the high dose of 3 g/kg/day (40 times the maximum projected human dose) was associated with proliferative findings in the transitional epithelium of the urinary tract. Urinary bladder transitional papilloma and carcinoma were also observed in the high dose males. These changes, together with inflammatory cell infiltrations, mineral deposition and hemorrhage, are judged to represent a reactive irritant inflammatory and hyperplastic response to the abnormal crystalline deposits evident in the urine as well as the systemic mineral imbalance occurring in these animals and not a carcinogenic effect of sevelamer hydrochloride.

## **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<sub>1</sub> generation or on the survival and development of the F<sub>2</sub> generation pups at doses tested ( $\leq$  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, and abnormal bone growth) 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. These doses are 60 to 140 times the maximum projected human dose of 75 mg/kg/day. In one study, sevelamer produced an increased incidence of submucosal edema of the stomach in female rats; the etiology of this finding is unclear. In dogs, sevelamer produced minimal signs of toxicity. Decreased red blood cell indices and decreased levels of vitamins D and E were observed in animals administered 2 g/kg/day. No overt signs of clinical toxicity and no drug-associated histopathological findings were observed at doses up to 2 g/kg/day.

In the segment II studies in rats and rabbits, there was no evidence that sevelamer directly induced embryoletality, 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 15 and 45 times the recommended human dose based on mg/kg), sevelamer caused reduced or irregular ossification of fetal bones, probably due to a reduced absorption of fat-soluble vitamin D. In rabbits, sevelamer slightly increased prenatal mortality due to an increased incidence of early resorptions at a dose of 1 g/kg/day (approximately 10 times the recommended human dose based on mg/kg). This was attributed to the increased requirements for vitamins and other nutrients in pregnancy.

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

## REFERENCES

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## PART III: CONSUMER INFORMATION

<sup>Pr</sup>Renagel®  
Sevelamer hydrochloride tablets

This leaflet is part III of a three-part “Product Monograph” published when RENAGEL was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about RENAGEL. 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 renal disease undergoing dialysis (whether hemodialysis or peritoneal dialysis).

#### What it does:

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

#### When it should not be used:

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

#### What the medicinal ingredient is:

Sevelamer hydrochloride

#### What the nonmedicinal ingredients are:

colloidal silicon dioxide; diacetylated monoglyceride; hypromellose; iron oxide black ink; isopropyl alcohol; propylene glycol; and stearic acid.

#### What dosage forms it comes in:

800 mg tablets

### WARNINGS AND PRECAUTIONS

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

**BEFORE** you use RENAGEL talk to your doctor or pharmacist if you:

- have an intestinal disorder such as, difficulty swallowing, or conditions that slow down the passage of food through the intestine and lead to blockage.
- have had surgery on your intestines.
- have a bowel obstruction/blockage.

- have severe 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

Drugs that may interact with RENAGEL 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 RENAGEL.

### PROPER USE OF THIS MEDICATION

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

#### Usual starting dose:

Dosage is individualized. Your doctor will determine your dosage.

RENAGEL 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: Approximately nine 800 mg tablets per day (equivalent to three 800 mg tablets per meal).

#### Overdose:

In case of an overdose, contact your doctor or 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 RENAGEL is generally well tolerated, some patients may experience side effects, including: nausea, vomiting, diarrhea, indigestion, constipation, rash and itch.

**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	
<b>Common</b>	Abdominal pain		✓	
<b>Very rare</b>	Intestinal blockage, obstruction or hole in the intestine (symptoms include: abdominal discomfort, cramping and gas pains, difficulty passing stools, nausea/vomiting especially after meals, excessive burping; later symptoms include fever and chills)			✓

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

**HOW TO STORE IT**

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

Keep out of reach of children.

**REPORTING SUSPECTED SIDE EFFECTS**

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

By toll-free telephone: 866-234-2345  
 By toll-free fax: 866-678-6789  
 Online: [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)  
 By email: [CanadaVigilance@hc-sc.gc.ca](mailto:CanadaVigilance@hc-sc.gc.ca)

By regular mail:  
 Canada Vigilance National Office  
 Marketed Health Products Safety and Effectiveness Information Bureau  
 Marketed Health Products Directorate  
 Health Products and Food Branch  
 Health Canada  
 Tunney's Pasture, AL 0701C  
 Ottawa ON K1A 0K9

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.

**MORE INFORMATION**

This document plus the full product monograph, prepared for health professionals can be found at: [www.genzyme.ca](http://www.genzyme.ca) or by contacting the sponsor, Genzyme Canada Inc., at: 1-877-220-8918

This leaflet was prepared by Genzyme Canada Inc.

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