PRODUCT MONOGRAPH

PrRenagel® Tablets
sevelamer hydrochloride
800 mg tablets
400 mg tablets

PrRenagel® Capsules
sevelamer hydrochloride capsules
403 mg capsules

Phosphate binder

Genzyme Canada Inc.
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Control# 083067

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ACTION AND CLINICAL PHARMACOLOGY

1. General

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.

Renagel® (sevelamer hydrochloride) is a nonabsorbed polymer phosphate binder. When taken with meals Renagel® inhibits intestinal absorption of ingested phosphate. It prevents hyperphosphatemia when administered to patients with End Stage Renal Disease (ESRD) on hemodialysis.

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**.**

2. Short-Term Clinical Trials

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. 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.

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

2a. 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

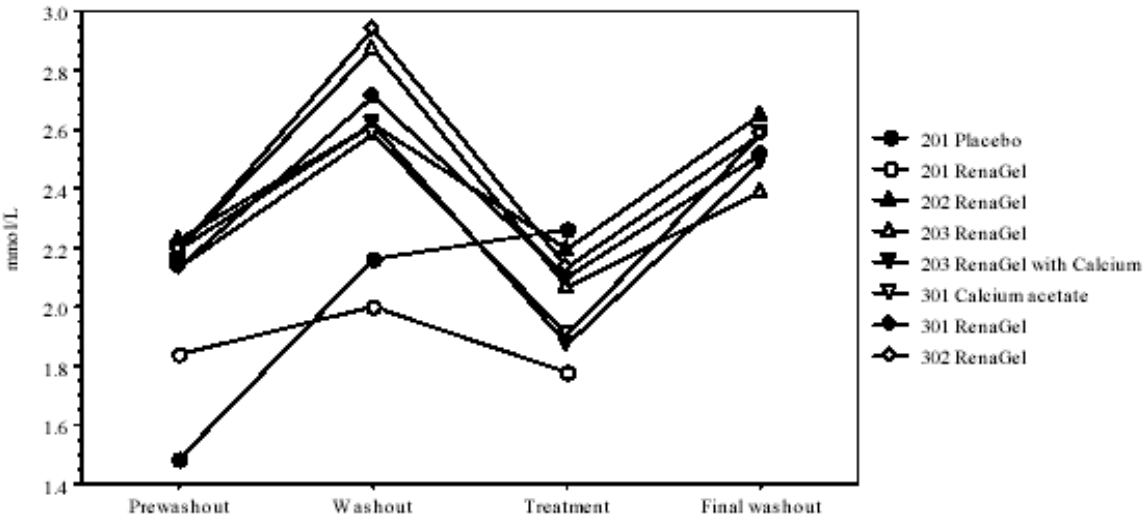
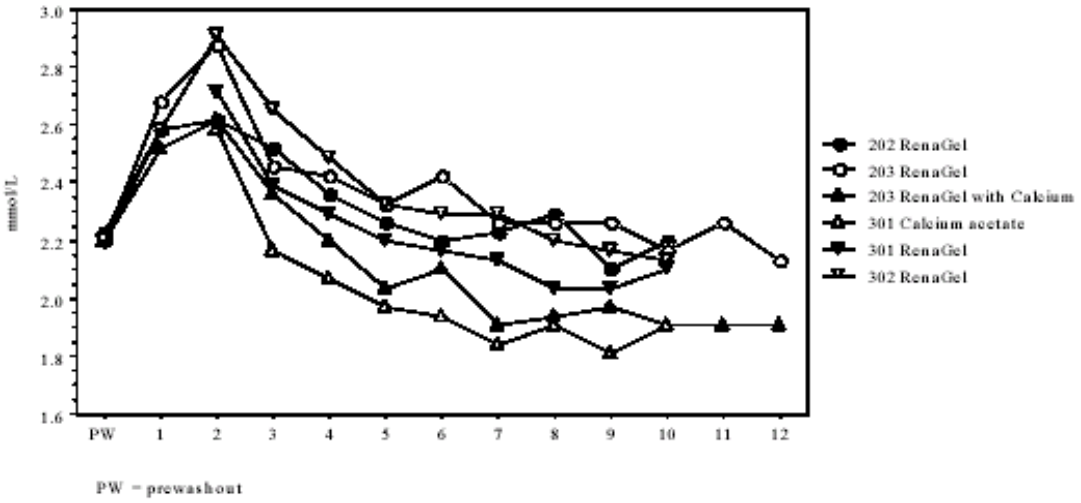


Figure 2: Changes in Serum Phosphorus on a Weekly Basis in Patient Studies



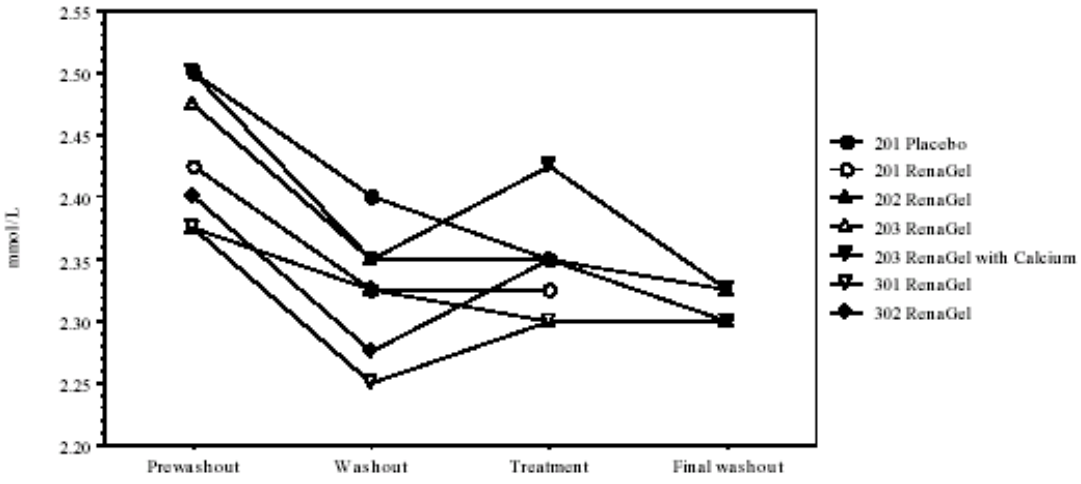
PW = prewashout

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.

2b. Calcium

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

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

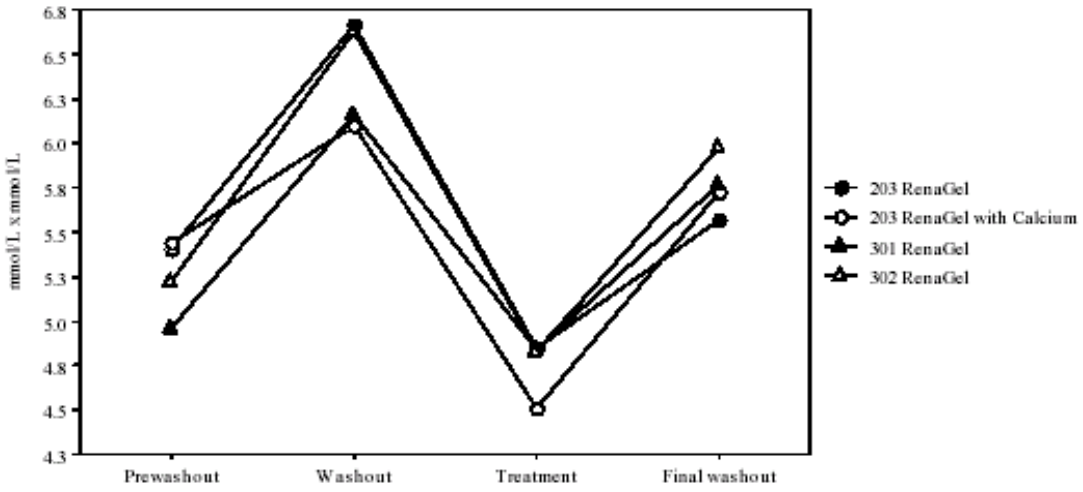


Withdrawal from calcium phosphate binder and subsequent treatment of the same patients with Renagel® has lowered the incidence of hypercalcemic events (serum Ca > 2.75 mmol/L) from 22% to 5%.

2c. 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.

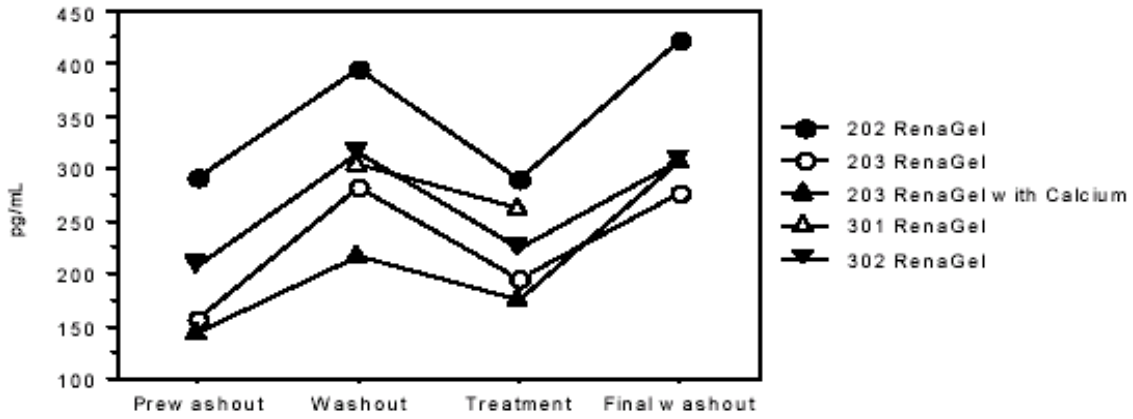
Figure 4: Mean Serum Calcium x Phosphorus Product (mmol/L x mmol/L) Over Time



2d. 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.

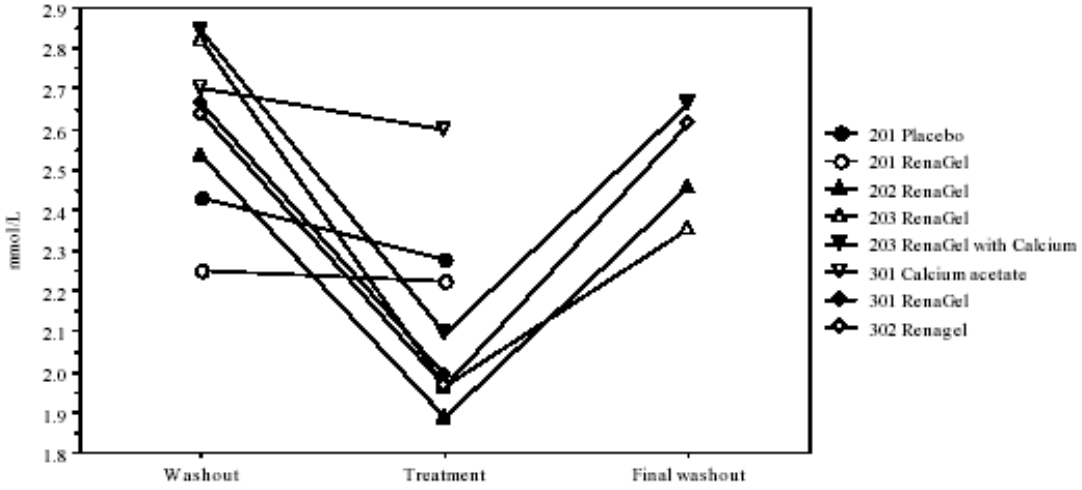
Figure 5: Median Intact Parathyroid Hormone Concentration (pg/mL)



2e. 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)



3. Long-Term Clinical Trials

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, Renagel® and Calcium both significantly decreased mean serum phosphorous by over 0.65 mmol/L.

There were no significant change in the levels of lipid soluble vitamins A, D, E (but not that of folic acid) during a 44-week study.

INDICATIONS AND CLINICAL USE

Renagel® (sevelamer hydrochloride) is indicated for the control of hyperphosphatemia in patients with ESRD (End Stage Renal Disease) on hemodialysis.

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

Since Renagel® (sevelamer hydrochloride) expands in water, capsules should not be taken apart prior to administration and should not be chewed. Renagel® 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 ESRD patients who are not on hemodialysis have not been studied.

PRECAUTIONS

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

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

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

Use in the Elderly: No special considerations are needed for elderly patients.

Use in Children: 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.

Use in Obstetrics; Nursing Mothers: The safety of Renagel® has not been established in pregnant or lactating women. In preclinical studies, there was no evidence that Renagel® 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). Renagel® should only be given to pregnant women if the benefits outweigh the risks.

Drug Interactions: Renagel® 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, 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.

ADVERSE REACTIONS

In clinical trials, Renagel® (sevelamer hydrochloride) was well tolerated. The adverse events presented in the table below were reported on study but not necessarily attributed to Renagel® treatment. The incidences of these events were not dose related.

Adverse events reported in $\geq$10% of patients for all Renagel® studies (N = 483 patients) is provided in the table below. For these events, in a parallel design study with treatment duration of 52 weeks, adverse events reported for Renagel® tablets (N=99) were similar to those reported for calcium (calcium acetate and calcium carbonate) (N=101).

Adverse Events in all Renagel®		Trials Adverse Events from a Parallel Design Study of Renagel® vs Calcium (calcium acetate and calcium carbonate)	
		GTC-49-301	
System Organ Class Event	Renagel® N = 483 **%**	Renagel® N = 99 **%**	Calcium N = 101 **%**
Gastrointestinal Dis orders			
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			
Mechanical Complication of Implant	4.3	6.1	10.9
Pyrexia	8.7	5.1	10.9

* Statistically significant

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Since Renagel® (sevalamer 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 15.3 grams.

DOSAGE AND ADMINISTRATION

The criteria for initiating Renagel® in patients not using another phosphate binder are outlined below:

Starting Dose		
Serum Phosphorus	**Renagel® Tablets 800 mg**	**Renagel® Tablets 400 mg or Renagel® Capsules 403 mg**
> 1.8 and < 2.4 mmol/L	3 tablets per day (2.4 grams)	6 tablets or capsules per day (2.4 grams)
≥ 2.4 and < 2.9 mmol/L	6 tablets per day (4.8 grams)	9 tablets or capsules per day (3.6 grams)
≥ 2.9 mmol/L	6 tablets per day (4.8 grams)	12 tablets or capsules 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 or capsule 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.

The tablets or capsules should not be bitten, chewed or broken apart prior to dosing.

Renagel® should be taken immediately prior to or with meals. If a dose is forgotten, it should be skipped.

Average Maintenance Dose: 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 15.3 grams.

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®).

PHARMACEUTICAL INFORMATION

Drug Substance
Common 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)

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.

Molecular Weight: $(C_3H_7N \bullet nHCl)_{812z}(C_9H_{18}N_2O \bullet nHCl)_{94z}$ 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.

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.

Composition

Renagel® Tablets**:** Sevelamer hydrochloride; hydroxypropyl methylcellulose; diacetylated monoglyceride; colloidal silicon dioxide; and stearic acid. The tablet imprint contains iron oxide black ink.

Renagel® Capsules: Sevelamer hydrochloride; colloidal silicon dioxide; stearic acid; titanium dioxide, E171; indigo carmine ink, E132; shellac and propylene glycol.

Stability and Storage Recommendations

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

AVAILABILITY OF DOSAGE FORMS

Renagel® 800 mg Tablets are supplied as capsule shaped, film-coated tablets, imprinted with "RENAGEL 800," containing 800 mg of sevelamer hydrochloride. Renagel® 800 mg Tablets are available in bottles of 180 tablets.

Renagel® 400 mg Tablets are supplied as capsule shaped, film-coated tablets, imprinted with "RENAGEL 400," containing 400 mg of sevelamer hydrochloride. Renagel® 400 mg Tablets are available in bottles of 360 tablets.

Renagel® Capsules are suppled as white, opaque, hard gelatin capsules, containing 403 mg of sevelamer hydrochoride, axially imprinted with G403. Renagel® Capsules are available in bottles of 200 capsules.

PHARMACOLOGY

The following column contains summary tables summarizing major findings from the pharmacology and toxicology studies.

Primary Therapeutic Activity: Listing of studies and summary of pharmacological effects							
Subject	*In vitro* Binding to Phosphate	Effects on Faecal Phosphorus Excretion	Effects of Renagel® and Calcium Carbonate on Faecal Phosphorus Excretion	Pilot Study: Model of Renal Secondary Hyperparathyroidism & Hyperphosphatemia	Effects on Mass Balance of Phosphorus Excretion in Normal Rats Fed a High Phosphorus Diet	Effect on Urinary Phosphorus Excretion	Effects on Bile Acid Mass Excretion in Fat Fed Hamsters
Duration	N/A	5 days	5 days	49 days	7 days	4 days	2 days
Species/ Strain	N/A	Wistar Rat	Wistar Rat	Sprague-Dawley Rat	Sprague-Dawley Rat	Sprague-Dawley Rat	Hamster
N	N/A	6 M cross-over	6 M cross-over	16 M	12 F cross-over	12 F	28 F
Dosage	N/A	0, 11.7% w/w	0, 11.7% w/w	0, 5, 7.5, 10% w/w	0, 8, 12% w/w	0, 0.5, 1.0, 3.0, 9.0% w/w	0, 0.2, 0.4, 0.6% w/w
Route/Form	N/A	Oral in diet	Oral in diet	Oral in diet	Oral in diet	Oral in diet	Oral in diet
Results	Renagel® exhibits theoretical binding capacity required to meet therapeutic objectives.	90% ↑ in faecal phosphorus excretion vs cellulose. 34.23 ± 5.67 mg/g vs 17.97 ± 2.09 mg/g.	77% ↑ in faecal phosphorus excretion vs cellulose & 23% ↑ vs calcium carbonate. 27.43 ± 2.42 mg/g vs 15.45 ± 3.79 mg/g vs 19.08 mg/g.	Renagel® suppresses PTH elevation in partially nephrectomized rats. The diff in PTH levels in control and Renagel® rats was significant ($p < 0.05$) on days 40 & 49.	Ratio of faecal to in urinary phosphorus excretion ↑ significantly ($p < 0.05$).	Renagel® produced a dose-dependent ↓ urinary phosphorus excretion. (56.6, 65.6, 87.6, 96.4% ↓ in urinary phosphorus respectively).	Renagel® produced a dose-dependent ↑ in bile acid mass excretion.

Pre-Clinical Pharmacokinetics Studies: Listing of studies and summary of pharmacological effects									
Subject	Degradation in GI Contents	Disposition and Excretion of Cross-Linked Polymer Hydrogel (CPH) [^{14}C]Renagel® in Rats	Absorption and Distribution after a Single Oral dose of [^{14}C]Renagel®	Excretion after a Single Oral dose of [^{14}C]Renagel®	Excretion after a Single Oral dose of [^{3}H]Renagel®	Absorption, Distribution and Excretion after a Single Oral dose of [^{3}H]Renagel®	Absorption, Distribution and Excretion	Open Balance Study of ^{14}C-Polyallylamine Renagel®	Absorption, Distribution and Excretion of Radioactivity of a Single Dose of [^{3}H]-Labeled Renagel® With and Without Renagel® Pretreatment via Feed for One Month
Duration	2 days	1 day	1 day	1 day	1 day	1 day	1 day	1 day	29 days
Species/ Strain	*In vitro*	Sprague-Dawley Rat	Sprague-Dawley Rat	Sprague-Dawley Rat	Sprague-Dawley Rat	Beagle/LRE Dog	Rat/Dog	Beagle Dog	Sprague-Dawley Rat
N	N/A	27 male	15 male	15 male	18 male	6 male	1 male each	6 male	12 male
Dosage	N/A	0.10 g/kg	0.25 g/kg	0.25 g/kg	0.25 g/kg	0.25 g/kg	0.25 g/kg	0.20 g/kg	6.0 g/kg and 0.25 g/kg
Route	N/A	Oral, gavage	Oral, gavage	Oral, gavage	Oral, gavage	Oral , capsule	Oral	Oral, capsule	Oral, gavage
Results	No significant decomposition occurred in GI contents.	Faeces 94.7%; Blood and urine 0.00%. See next table for more details.	None detected in blood, <0.005% in tissue.	Faeces 102.98%; urine 0.06%; Expired air 0.08%. See next table for more details.	Faeces 108.07%; Urine 0.04%; Expired air 0.01%. See next table for more details.	Faeces 93.62%; Urine 0.03%; Blood 0.00%. See next table for more details.	Rat: Excreted in faeces. Dog: Excreted in faeces, none detected in blood.	Faeces 97.33%; Blood 0.00%; Urine 0.06%. See next table for more details.	Single dose: Faeces 97.60%; Blood 0.01%; Urine 0.05%. After 1 month: Faeces 104.65%; Blood 0.01%; Urine 0.05%. See next table for more

									details.

Total Recovery of Radioactivity from Rats and Dogs Administered Radiolabelled-Renagel®							
Duration	Single dose	Single dose	Single dose	28 days	Single dose	Single dose	Single dose
Species/Strain	Sprague-Dawley Rat	Beagle Dog	Sprague-Dawley Rat		Sprague-Dawley Rat	Beagle Dog	Sprague-Dawley Rat
N	6 + 21	6	6	6 + 3	15	6	18
Dosage	100 mg/kg	200 mg/kg	250 mg/kg	6 g/kg/d x 28d, then 250 mg/kg test	250 mg/kg	250 mg/kg	250 mg/kg
Route of Admin	Oral gavage	Oral capsule	Oral gavage		Oral gavage	Oral capsule	Oral gavage
Results	**Fraction of Dose (%)**						
Faeces	94.7 ± 5.4	97.33 ± 2.18	97.60 ± 6.22	104.65 ± 2.97	102.98 ± 4.47	93.62 ± 2.35	108.07 ± 3.32
GI Content	0.00 ± 0.00	0.07 ± 0.07	0.11 ± 0.23	0.01 ± 0.01	0.01 ± 0.01	0.27 ± 0.27	0.01 ± 0.00
GI Tissue	0.00 ± 0.00	0.05 ± 0.09	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01
Liver	0.00 ± 0.00	0.02 ± 0.04	0.00 ± 0.00	0.00 ± 0.00	Not Done	0.00 ± 0.00	Not Done
Kidney	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	Not Done	0.00 ± 0.00	Not Done
Skeletal Muscle	Not Done	Not Done	0.05 ± 0.01	0.05 ± 0.01	Not Done	0.00 ± 0.00	Not Done
Urine	0.00 ± 0.00	0.06 ± 0.08	0.05 ± 0.00	0.05 ± 0.01	0.06 ± 0.01	0.03 ± 0.02	0.04 ± 0.00
Blood	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.00	0.01 ± 0.00	Not Done	0.00 ± 0.00	Not Done
Cage Wash	0.00 ± 0.00	Not Done	0.00 ± 0.00	0.00 ± 0.00	Not Done	0.00 ± 0.00	Not Done
Expired Air	Not Done	Not Done	Not Done	Not Done	0.08 ± 0.01	Not Done	0.01 ± 0.00
Carcass	Not Done	Not Done	Not Done	Not Done	0.00 ± 0.00	Not Done	0.20 ± 0.03

Pre-Clinical Drug Interaction Studies: Listing of studies and brief summary of results		
Subject	Effect on the Oral Bioavailability of ^{125}I-L-Thyroxine, ^{3}H-Digoxin, ^{3}H-Estrone, and ^{3}H-Propranolol	Effect on the Oral Bioavailability of ^{3}H-Tetracycline, ^{3}H-Verapamil, ^{3}H-Quinidine, ^{3}H-Valproic Acid, Dihydroxy Vitamin D_3 and ^{14}C-Warfarin
Duration	1 day	1 day
Species/ Strain	Beagle Dog	Beagle Dog
N	8 male	8 male
Dosage	0.10 g/kg	0.10 g/kg
Route/ Form	Oral, capsule	Oral, capsule
Results	No effect on C_{max} or AUC for estrone, propranolol, digoxin, or thyroxine. Increased t_{max} for estrone and propranolol. See next table for detailed results.	No effect on C_{max}, t_{max}, or AUC for tetracycline, verapamil, quinidine, valproic acid, dihydroxy vitamin D_3 or warfarin. See next table for detailed results.

Beagle Dog Drug Interaction Study Results			
Test Article /Vehicle	**Total Radioactivity**		
	t_{max}(hours)	**C_{max} (µg eq/mL)**	**AUC_{0-48} (µg eq.h/mL)**
^{3}H-digoxin /80% ethanol	3.1 ± 2.2[a]	3.905 ± 3.3847	39.3 ± 15.12
^{3}H-digoxin and Renagel®	2.6 ± 2.1[b]	3.089 ± 2.0827[b]	37.4 ± 16.88[b]
^{3}H-estrone /anhydrous ethanol	1.3 ± 1.2	21.681 ± 9.4670	187.4 ± 90.33
^{3}H-estrone and Renagel®	5.0 ± 4.2	22.823 ± 14.5855	270.6 ± 144.04
^{3}H-propranolol /anhydrous ethanol	2.8 ± 3.8	1.159 ± 0.1833	20.5 ± 2.19
^{3}H-propranolol and Renagel®	4.2 ± 2.8[b]	1.066 ± 0.2779[b]	21.2 ± 2.01[b]
^{125}I-L-thyroxine /anhydrous ethanol	7.9 ± 4.1	5.570 ± 1.6367	136.9 ± 28.57
^{125}I-L-thyroxine and Renagel®	8.6 ± 3.4[b]	5.154 ± 1.0673[b]	139.3 ± 24.65[b]
^{3}H-tetracycline /deionized water	1.2 ± 0.5	1.534 ± 0.626	30.8 ± 12.9
^{3}H-tetracycline and Renagel®	1.6 ± 1.1	1.490 ± 0.750	25.7 ± 13.1
^{3}H-verapamil /anhydrous ethanol	7.5 ± 7.7	3.979 ± 0.801	161.0 ± 24.9
^{3}H-verapamil and Renagel®	5.0 ± 3.8	4.060 ± 0.785	164.1 ± 28.7
^{3}H-quinidine /anhydrous ethanol	2.1 ± 0.8	5.135 ± 1.932	56.3 ± 26.1
^{3}H-quinidine and Renagel®	3.4 ± 2.4	4.552 ± 2.183	53.5 ± 26.3
^{3}H-valproic acid /ethanol:water (4:1 v/v)	2.0 ± 2.5	27.04 ± 12.48	433.8 ± 64.7
^{3}H-valproic and Renagel®	2.4 ± 3.9	27.62 ± 11.96	429.0 ± 75.6
Dihydroxy vitamin D_3 /anhydrous ethanol	3.4 ± 2.2	240.9 ± 125.9	3289 ± 390
Dihydroxy vitamin D_3 and Renagel®	2.9 ± 1.2	180.5 ± 30.9	3064 ± 396

^{14}C-warfarin /anhydrous ethanol	6.9 ± 3.9	1.938 ± 0.279	45.4 ± 3.9
^{14}C-warfarin and Renagel®	7.9 ± 3.2	2.024 ± 0.259	45.4 ± 3.3

a = mean ± SD, N = 8; b = mean ± SD, N = 7

TOXICOLOGY

Pre-Clinical Toxicology: Listing of Repeat-Dose studies and summary of toxicology effects CONTINUED ON NEXT PAGE						
Duration	28 days	1 month	28 days	12 weeks	90 days	13 & 26 weeks
Species/Strain	Hsd:SD Rat	Slc Rat	Crl:CD Rat	SD Rat	Hsd:SD Rat	Hsd:SD Rat
N	80 (10F, 10 M/grp)	150 (15F, 15M/grp)	80 (10F, 10M/grp)	32 (4F, 4M/grp)	150 (15F, 15M/grp)	160 (20F, 20M/grp)
Dosage	1.0, 4.5, 10.0 g/kg; 10.0 g/kg cellulose	0.03, 1.0, 3.0, 10.0 g/kg; 10.0 g/kg cellulose	1.0, 4.5, 10.0 g/kg; 10.0 g/kg cellulose	Range-finding study 0.6, 2.0, 6.0 - 7.0 g/kg; 6.0 g/kg cellulose	1.0, 2.0, 4.5, 10.0 g/kg; 10.0 g/kg/d cellulose	0.6, 3.0, 6.0 g/kg; 6.0 g/kg/d cellulose
Route/Form	Oral, diet	Oral, diet	Oral, diet	Oral, diet	Oral, diet	Oral, diet
Results	NOAEL = 1g/kg. In the high dose male: anaemia, ↓ vitamins D & E and haemorrhagic syndrome was observed.	NOAEL = 1g/kg. In the high dose male and female: anaemia, ↑ GPT, alkaline phosphatase and ↓ total protein, P, K, and vitamin E were observed.	NOAEL = 1g/kg. High dose male: anaemia, prolonged coagulation times; ↓ food consumption, body weight gains,↓ in vitamins D, E & K were observed. 8M in 10 g/kg grp found dead or moribund sacrificed	↑ food consumption were observed in the high dose male.	The NOAEL was 4.5g/kg. In the high dose, ↓ in vitamins D & E and organ weight change in spleen, liver, kidney and heart were observed. 3M in 10/g/kg grp were found dead or	In the mid and high-dose groups there was a ↓ in vitamins D & E. Minimal submucosal gastric edema with no histopathological damage observed in all groups.

Pre-Clinical Toxicology: Listing of Repeat-Dose studies and summary of toxicology effects CONTINUED ON NEXT PAGE						
			prior to study termination. Effects probably due to vitamins D & K deficiency. 4.5 & 10 g/kg males: physeal dysplasia femur. 10 g/kg males physeal dysplasia sternebrae. Both consistent with early changes seen in vitamin D deficiency.		moribund sacrificed prior to study termination probably as a result of vitamin K deficiency.	

Pre-Clinical Toxicology: Listing of Repeat-Dose studies and summary of toxicology effects CONTINUED FROM PREVIOUS PAGE					
Duration	28 days	28 days	1 month	13 weeks	1 year
Species/Strain	Dog	Beagle Dog	Dog	Beagle Dog	Beagle Dog
N	16 (4F/grp)	32 (4F, 4M/grp)	36 (6F, 6M/grp)	32 (4F, 4M/grp)	40 (6F, 6M/grp + 4F, 4M)
Dosage	1.2, 4.0, 12.0 g/kg; 12 g/kg/d cellulose	0, 0.2, 1.0, 2.0 g/kg	0, 0.6, 2.0 g/kg	0.2, 1.0, 2.0 g/kg	0, 0.2, 0.60, 2.0 g/kg
Route/Form	Oral, diet	Oral, capsule	Oral, capsule	Oral, capsule	Oral, capsule
Results	Serum calcium was decreased in the high-dose. Serum chloride was increased in the mid and high-dose.	In the high-dose decreases in vitamins D, E and iron were observed. In the mid and high-dose, decreases in urinary urobilinogen were seen. Dose related decrease in triglycerides and cholesterol.	The NOAEL was 0.6 g/kg. In the high-dose male and female, there was a decrease in total cholesterol, free cholesterol, phospholipid and serum vitamin E and an increase in water consumption and urinary calcium and chloride.	In the high-dose, decreases in cholesterol/triglyceride concentrations and decreases in serum vitamins D & E and increases in urinary calcium and chloride were observed.	The NOAEL was 0.6 g/kg. Renagel® produced no dose limiting toxicity at doses up to 2 g/kg/d. In the high-dose, there was a decrease in cholesterol, phospholipids, triglycerides, vitamins D, E and folic acid. Relative kidney weights were increased in the high dose.

Pre-Clinical Toxicology: Listing of Genotoxicity studies and summary of results				
Subject	*Salmonella typhimurium* Reverse Mutation Assay	Reverse Mutation Test	*In Vitro* Mammalian Cytogenetic Test	Micronucleus Cytogenetic Assay in the Mouse
Duration	N/A	N/A	N/A	2 days
Species/Strain	Ames Test	Bacterial Reverse Mutation Test	Chromosome Aberration	Mouse
N	N/A	N/A	N/A	5 female, 5 male
Dosage	5 mg/mL	5 mg/plate	5 mg/mL	572, 1144, 2286 mg/kg/d
Route/Form	N/A	N/A	N/A	Intraperitoneal
Results	Renagel® produced same mean # of revertants as the negative control in all strains ± metabolic activation. Renagel® was found non- mutagenic.	No antibacterial activity was observed. Renagel® was found non-mutagenic.	Renagel® was found to be weakly positive for the induction of structural chromosome aberration and negative for the induction of numerical chromosome aberration.	Renagel® was negative in the mice micronucleus assay.

Pre-Clinical Toxicology: Listing of Reproductive Toxicity studies and results				
Subject	Fertility	Teratology	Range-Finding Teratology	Teratology
Duration	Males: -4 weeks through mating. Females: -2 weeks to Day 7 Gestation	Days 6-17 of gestation	Days 7-19 of gestation	Days 6-18 of gestation
Species/Strain	Rat	Rat	Rabbit	Rabbit
N	200 (20F, 20M/grp)	125 (25F/grp)	25 (5F/grp)	117* (22F/grp, + 29F)
Dosage	0, 0.5, 1.5, 4.5 g/kg; 4.5 g/kg/d cellulose	0, 0.5, 1.5, 4.5 g/kg; 4.5 g/kg/d cellulose	0, 0.15, 0.5, 1.5 g/kg	0, 0.1, 0.5, 1.0 g/kg; *29F in 1.0 g/kg grp
Route/Form	Oral, diet	Oral, diet	Oral, gavage	Oral, gavage
Results	Male and female fertility and	No maternal toxicity. No	There were no treatment-	No maternal toxicity. No

	embryonic development NOAEL $\geq$ 4.5g/kg .	evidence of embryolethality or teratogenicity. Increase incidence of minor fetal skeletal abnormalities due to transitory changes in ossification rates; not indicative of fetotoxicity.	related changes.	evidence of embryolethality, fetotoxicity or teratogenicity. NOAEL $\geq$ 1.0g/kg.

Pre-Clinical Toxicology: Listing of Carcinogenicity studies and results		
Subject	Carcinogenicity	Carcinogenicity
Duration	104 weeks	104 weeks
Species/Strain	CD-1 Mouse	Charles River Sprague-Dawley CD Rats
N	100 (50F, 50M/grp)	100 (50F, 50M/grp)
Dosage	0, 5000, 20000, 50000 ppm	0, 0.3, 1.0, and 3.0 g/kg/day
Route/Form	Orally (diet)	Orally (diet)

Results	Mortality, survival time and clinical observations were similar in all treatment groups. Decreased body weights in high dose male and female mice were observed through most of study. Increased incidence of lymphomas in high dose females when compared to one of two concurrent control groups. No significant difference from the other control group. Dose is approximately 60X multiple of maximum projected human dose. Findings are of questionable biological significance and no significance to human use of the drug. No other significant treatment-related findings.	Mortality, survival time, and clinical observations were similar across groups. Decreased body weights, vitamin D and vitamin E levels, increased hemoglobin, hematocrit, red blood cells, and plasma and urine calcium observed in high dose males. Renal findings were transitional cell hyperplasia, increased transitional epithelial mineralization, pelvic inflammatory cell infiltrate, and pelvic hemorrhage in high dose males. High dose females showed increased incidence of pelvic hemorrhage. No other significant treatment-related histological findings.

REFERENCES

Bleyer AJ, Burke SK, Dillon M, Garrett B, Kant KS, Lynch D, *et al.* A Comparison of the Calcium-Free Phosphate Binder Sevelamer Hydrochloride With Calcium Acetate in the Treatment of Hyperphosphatemia in Hemodialysis Patients. *Am J Kidney Dis* 1999;33:694-701.

Burke SK, Amin NS, Incerti C, Plone MA, Lee JW. Sevelamer hydrochlroide (Renagel), a phosphate-binding polymer, does not alter the pharmacokinetics of two commonly used antihypertensives in healthy volunteers. *J Clin Pharmacol* 2001;41:199-205.

Burke SK, Slatopolsky EA, Goldberg DI. Renagel®, a novel calcium- and aluminum-free phosphate binder, inhibits phosphate absorption in normal volunteers. *Nephrol Dial Transplant* 1997;12:1640-4.

Chertow GM, Burke SK, Dillon MA, Slatopolsky E. Long-term effects of sevelamer hydrochloride on the calcium x phosphate product and lipid profile of haemodialysis patients. *Nephrol Dial Transplant* 1999;14:2907-2914.

Chertow GM, Dillon M, Burke SK, *et al*. A randomized trial of sevelamer hydrochloride (RenaGel) with and without supplemental calcium. Strategies for the control of hyperphosphatemia and hyperparathyroidism in hemodialysis patients. *Clin Nephrol* 1999;51:18-26.

Goldberg DI, Dillon MA, Slatopolsky EA, *et al*. Effect of RenaGel, a non-absorbed, calcium-and-aluminum-free phosphate binder, on serum phosphorous, calcium, and intact parathyroid hormone in end-stage renal disease patients. *Nephrol Dial Transplant* 1998;13:2303-10.

Plone M, Peterson J, Rosenbaum D, Burke S. Sevelamer, a phosphate-binding polymer, is a non-absorbed compound. *Clin Pharmacokinetic* 2002;41:517-23.

Pruchnicki Maria C, Coyle James D, Hoshaw-Woodard S, Bay William H. Effect of phosphate binders on supplemental iron absorption in healthy subjects. *J Clin Pharmacol* 2002;42:1171-6.

Rosenbaum DP, Holmes-Farley SR, Mandeville WH, Pitruzzello M, Goldberg DI. Effect of Renagel®, a non-absorbable, cross-linked, polymeric phosphate binder, on urinary phosphorus excretion in rats. *Nephrol Dial Transplant* 1997;12:961-4

Slatopolsky E, Burke S, Dillon M. RenaGel®, a nonabsorbed calcium-and-aluminum-free phosphate binder, lowers serum phosphorus and parathyroid hormone. *Kidney Int* 1999;55:299-307.