National PBM Drug Monograph
Sevelamer Hydrochloride (Renagel®)
VHA Pharmacy Benefits Management Strategic Healthcare Group
and the Medical Advisory Panel

Introduction

Patients with end-stage renal disease (ESRD) lose the ability to maintain phosphorus and calcium balance and can develop hyperphosphatemia, a condition that is associated with severe complications including metastatic calcifications, secondary hyperparathyroidism, calciphylaxis (vascular/cutaneous lesions or eruptions), and has been related to an increase in mortality due to coronary artery disease and sudden death.[1] The exact mechanisms of these morbidities are unclear but likely due to elevated serum phosphorus and elevated calcium x phosphorus products. Patients with an elevated calcium x phosphorus product can develop peripheral and cardiac calcification that may lead to conduction disturbances, arrhythmia, and sudden death.[2]

In order to assess the level of serum phosphorus and its effect on mortality in 6,407 patients on hemodialysis for at least one year, data from the US Renal Data System (USRDS) Case Mix Adequacy Study (CMAS) and the Dialysis Morbidity and Mortality Study Wave 1 (DMMS) were examined. A serum phosphorus level of > 6.5 mg/dl was found in over 39% of patients. The relative mortality risk was found to be 13% higher in patients with serum phosphorus between 6.6-7.8 mg/dl compared to those with 4.6-5.5 mg/dl (reference range). The relative mortality risk increased to 34% in patients with serum phosphorus between 7.9-16.9 mg/dl. The adjusted relative risk of mortality in patients with a serum phosphorus level greater than 6.5 mg/dl was 27% higher compared to patients with a level of 2.4-6.5 mg/dl ($P<0.001$). One explanation for the increased mortality associated with an elevated phosphorus level is the association with an elevated calcium x phosphorus product. The DMMS data was used to evaluate the effect of the calcium x phosphorus product on mortality risk. It was found that a calcium x phosphorus product > 72 mg^2/dl^2 was associated with a 34% higher relative mortality risk compared to patients with a calcium x phosphorus product within the reference range of 42 and 52 mg^2/dl^2 ($P<0.01$).[3]

According to the 1997 USRDS, 45% of patients on dialysis die from cardiovascular disease.[3] Soft tissue and vascular calcifications have been associated with an increased risk of morbidity and mortality in hemodialysis patients, especially for cardiovascular disease.[2,4] Recent studies have demonstrated an association between excessive calcium intake and coronary artery calcification in ESRD patients.[5,6] Cardiovascular disease has been found in adult patients with ESRD on hemodialysis more commonly than normal subjects of the same age group.[7] It has also been suggested that the morphology of the coronary plaque is different in patients with ESRD compared to controls with coronary artery disease in that patients with ESRD have significantly more calcified plaques.[8] There also may be a difference in the location of intracardiac calcification in patients with ESRD compared to older patients without renal failure.[9] To assess the extent of cardiovascular disease in younger patients with ESRD, 39 patients with ESRD on hemodialysis (mean age 19 $\pm$ 7 years) were compared to 60 normal subjects (age 20 to 30 years). Electron beam tomography (EBT) was used to screen for coronary artery calcification. The patients less than 20 years of age did not show evidence of coronary artery calcification although it was seen in 14 of the 16 patients who were 20 to 30 years of age. The mean calcification score was 1157 $\pm$ 1996 in these patients. Other researchers have suggested that calcification scores between 100 and 400 are associated with nonobstructive coronary artery disease and those with a score > 400 are more likely to have obstructive coronary artery disease.[10] Calcification was found in only 3 of the normal subjects. The calcification scores for these patients were 1, 2, and 77, respectively. Patients with calcification had been on dialysis longer (14 $\pm$ 5 years) compared to those patients without calcification (4 $\pm$ 4 years, $P<0.001$). Patients with calcification also had a higher serum phosphorus level (6.9 $\pm$ 0.9 mg/dl vs. 6.3 $\pm$ 1.2 mg/dl, $P=0.06$) and significantly higher calcium x phosphorus product (65.0 $\pm$ 10.6 mg^2/dl^2 vs.

56.4 ± 12.7 mg^2/dl^2, P=0.04). Serum calcium and parathyroid hormone (PTH) were not different between the two groups. The dose of calcium was higher in patients with calcification compared to those without (6456 ± 4278 mg/d vs. 3325 ± 1490 mg/d, P=0.02).[5]

Recently published guidelines recommend serum phosphorus < 5.5 mg/dl and calcium x phosphorus product < 55 mg/dl.[11-13] Increased PTH can lead to osteitis fibrosa cystica (a form of renal osteodystrophy associated with significant morbidity).[2,14-16] A decrease in phosphorus has been shown to decrease serum PTH levels.[2,14,15]

Serum phosphorus levels are maintained by dietary restriction of phosphate to less than 1 gram/day, inhibition of intestinal phosphate absorption with either a calcium acetate, calcium carbonate, or aluminum hydroxide phosphate binder, and dialysis.[17] Oral calcium acetate and calcium carbonate are often used as a phosphate binder, but their use is limited by a high incidence of constipation, nausea, hypercalcemia, and an increased risk for metastatic vascular calcifications.[18] Aluminum-containing salts are also effective phosphate-lowering agents, but their use is limited by reports of aluminum toxicity such as osteomalacia, myopathy, anemia, and dementia.[17] Therefore, an effective phosphate-binder with minimal side effects compared with the aluminum or calcium binders would be a potential alternative for use in patients with ESRD without the complications of cardiac calcification or aluminum toxicity.

In the VHA Clinical Practice Guidelines for the Management of Chronic Renal Disease and Pre-ESRD in the Primary Care Setting, the Management of Renal Failure Working Group states that sevelamer hydrochloride (Renagel®) may be used for lowering phosphate in patients with ESRD on dialysis "but its high cost and recent introduction will probably limit its use to Nephrology Service." (Reference: Slatopolsky et al., 1999[14]; Evidence: QE=II, SR=A)[19]

The Food and Drug Administration has approved sevelamer hydrochloride (Renagel®), a nonabsorbed calcium-free, aluminum-free phosphate binder for lowering serum phosphorus in patients with ESRD on hemodialysis. Sevelamer, when taken with meals has been shown to decrease serum phosphorus levels in patients with ESRD who are on hemodialysis, while decreasing the incidence of hypercalcemic episodes relative to patients on calcium acetate treatment. The safety and efficacy of sevelamer hydrochloride in ESRD patients who are not on hemodialysis has not been studied.[14,18,20] The potential advantage of sevelamer is by reducing total calcium intake in a population of patients who cannot eliminate excessive calcium because of renal disease[21] (refer to Table below), and thus reducing the risk of cardiac calcification.

Estimated Calcium Balance in Patients with ESRD[22]

Subject	In	Absorbed	Binder	Dialysis influx	Balance (g/wk)
Normal	7.0	2.5			0
ESRD	4.2	0.6		0	0.6
HD	4.2	0.6		2.6	3.2
Binder	25.2	3.3	21	2.6	5.9
Binder + D	25.2	4.0	21	2.6	6.6
PD	4.2	0.6		0.4	1.0
Binder	25.2	3.3	21	0.4	3.7
Binder + D	25.2	4.0	21	0.4	4.4

In a recent clinical trial sponsored by the manufacturer, 200 hemodialysis patients were randomized to sevelamer 800mg or calcium-based phosphate binders (calcium acetate 667mg at U.S. sites; calcium carbonate 500mg at sites in Europe) for one year. Doses were titrated to achieve target serum phosphorus (3.0 to 5.0 mg/dL) and target calcium (8.5 to 10.5 mg/dL) during the first 12 weeks. Thereafter, vitamin D and the dialysate calcium concentration could also be adjusted to these target levels as well as a target range for intact PTH (150 to 300 pg/mL). The average dose of sevelamer was 6.5 ± 2.9 gm/day (≈ eight 800 mg tablets), calcium acetate 4.6 gm/day (≈ seven 667 mg tablets), and calcium carbonate 3.9 gm/day (≈ eight 500 mg

tablets). Serum phosphorus was similar in both treatment groups (5.1 ± 1.2 mg/dL and 5.1 ± 1.4 mg/dL for sevelamer and calcium, respectively). Serum calcium was significantly higher in the calcium treatment group (9.7 ± 0.7 mg/dL) compared to treatment with sevelamer (9.5 ± 0.6 mg/dL, p=0.002). There was no significant difference in calcium x phosphorus product or intact PTH, although more patients on calcium had intact PTH levels below target (p=0.001). Of interest, LDL-cholesterol was significantly lower in the sevelamer vs. calcium treatment group (65 ± 21 mg/dL vs. 103 ± 43 mg/dL, p<0.0001).[23] In another publication of a cross sectional analysis of these hemodialysis patients with baseline EBT, mean baseline coronary artery calcium scores were associated with myocardial infarction (p<0.0001) and angina (p<0.0001).[10] In the present study, mean baseline coronary artery calcium scores were not significantly different (1712 ± 2901 and 1125 ± 1583 in the sevelamer and calcium treatment groups, respectively). The absolute change in calcification score from baseline as measured in the coronary arteries was –46 ± 692 with sevelamer and 151 ± 471 with calcium (p=0.04). In the aorta, the change in calcification score was –532 ± 1706 compared to 185 ± 3100 (p=0.01) in the sevelamer and calcium treatment groups, respectively. The authors concluded that sevelamer reduced the progression of coronary and aortic calcification compared to treatment with calcium-based phosphate binders.[23] Whether or not this translates into a difference in outcomes remains uncertain since others have found coronary calcification in hemodialysis patients to be associated with more favorable outcomes (i.e., revascularization, myocardial infarction, or death, p=0.06) after percutaneous coronary intervention than patients without calcification.[24]

The risk of hospitalization was evaluated in a case-control study of 152 Medicare patients with ESRD on hemodialysis treated with sevelamer compared to 152 Medicare patients with ESRD receiving conventional phosphate binders. Sevelamer treated patients were selected from those included in a long-term safety and efficacy trial of sevelamer. Patients were matched by age, gender, presence of diabetes, and geographic location. Patients in the conventional treatment group had a higher incidence of stroke or transient ischemic attack, and gastrointestinal disease with bleeding than the sevelamer group. These differences were adjusted for in the comparative analysis and did not affect the difference in outcome. The relative risk of first hospitalization within a 17-month follow-up period was 46-54% less in patients on sevelamer compared to the case-control group (P=0.03). The mean dose of sevelamer at the end of the evaluation period was 5.3 g/d. At baseline, the average calcium x phosphorus product was 78 mg^2/dl^2 compared to 55 mg^2/dl^2 at the end of treatment. Total per-member per-month Medicare expenditures during the follow-up period were $1,400 less in patients treated with sevelamer compared to the control group (cost savings of approximately $16,500 per-year per-patient).[25]

Clinical Pharmacology

Sevelamer hydrochloride is an aluminum-free, calcium-free cross-linked poly[allylamine hydrochloride] cationic polymer that binds dietary phosphate ions within the gastrointestinal tract, limiting absorption and thereby reducing serum phosphate concentrations without altering calcium, aluminum, or bicarbonate concentrations. Sevelamer is resistant to digestive degradation and is not absorbed across the gastrointestinal tract. Sevelamer contains multiple amines spaced one carbon away from the polymer backbone that become partially protonated once in the intestinal tract and interact with phosphate ions by ionic and hydrogen bonding. Sevelamer also binds bile acids which has lipid-altering effects.[14,18,20]

Pharmacokinetics[15]

	Sevelamer	Calcium Acetate
Elimination	Feces 100%	Mainly in feces as unabsorbed calcium, 20% renally eliminated (assuming normal renal function)
Bioavailability	Not systemically absorbed, no gastrointestinal absorption.	Absorption from gastrointestinal tract requires Vitamin D; 30-40% absorption

FDA Approved Indication(s) and Off-label Uses

Sevelamer hydrochloride is indicated for the reduction of serum phosphorus in patients with ESRD on hemodialysis. The safety and efficacy of sevelamer in ESRD patients who are not on hemodialysis has not been studied.[15]

Current VA National Formulary Status

Sevelamer hydrochloride is currently not listed on the VA National Formulary.

Dosage and Administration[15]

Initial Adult Dose: 800 to 1600 mg three times a day with each meal depending on patient's initial serum phosphorus concentration. Table 1 describes initial recommended doses of sevelamer in patients currently not taking a phosphate binder.

Table 1. Starting Dose of Sevelamer Hydrochloride for Patients Not Taking a Phosphate Binder

SERUM PHOSPHORUS	Sevelamer 800 MG Tablets	Sevelamer 400 MG Tablets OR 403 MG Capsules
>6.0 and < 7.5 mg/dL	1 tablet three times daily with meals	2 tablets or capsules three times daily with meals
>7.5 and <9.0 mg/dL	2 tablets three times daily with meals	3 tablets or capsules three times daily with meals
>9.0 mg/dL	2 tablets three times daily with meals	4 tablets or capsules three times daily with meals

Patients Switching From Calcium Acetate. Clinical trials involving 84 ESRD patients on hemodialysis showed similar reductions in serum phosphorus with equivalent doses (mg for mg) of sevelamer capsules and calcium acetate. Table 2 shows the recommended initial doses of sevelamer based on a patient's current calcium acetate dose.

Table 2. Starting Dose for Patients Switching From Calcium Acetate to Sevelamer Hydrochloride

CALCIUM ACETATE 667 MG (TABLETS PER MEAL)	SEVELAMER 800 MG (TABLETS PER MEAL)	SEVELAMER 400 MG (TABLETS OR CAPSULES PER MEAL)
1 tablet	1 tablet	2 tablets or capsules
2 tablets	2 tablets	3 tablets or capsules
3 tablets	3 tablets	5 tablets or capsules

Dose Titration: The dose is adjusted gradually according to serum phosphorus concentrations by increasing or decreasing one capsule/tablet per meal every two weeks. The proper dose is that which lowers serum phosphorus to 6.0 mg/dL or less. The average dose in Phase 3 clinical trials was four 403 mg capsules per meal. The average dose used in a recent comparison trial with calcium-based binders was 6.5 $\pm$ 2.9 gm/day (≈ eight 800 mg tablets).[23] The maximum dose used in clinical trials was 12.1 grams or 30 capsules/day (the equivalent of 5 sevelamer 800 mg tablets per meal or 10 sevelamer 400 mg tablets per meal). Table 3 gives the dose titration guideline.

Table 3. Dose Titration Guideline

SERUM PHOSPHORUS	SEVELAMER DOSE
>6.0 mg/dL	Increase 1 tablet/capsule per meal at 2 week intervals
3.5-6.0 mg/dL	Maintain current dose
<3.5 mg/dL	Decrease 1 tablet/capsule per meal

Clinical trials evaluating drug interactions have been conducted and shown that sevelamer did not significantly alter the pharmacokinetic profiles of digoxin, warfarin, enalapril, or metoprolol.[26,27] When taking an oral medication where changes in blood concentrations could significantly effect drug safety or efficacy, the medication should be taken at least one hour before or three hours after sevelamer, or the physician should consider monitoring blood levels of the drug. (See PRECAUTIONS: Drug interactions.)

Sevelamer should not be used after expiration date on the bottle.

Auxiliary labeling: Take with meals, swallow capsules whole, do not break or chew.

Adverse Effects (Safety Data)

In a placebo-controlled, two-week trial, the incidence of adverse effects were similar between sevelamer capsules (N = 24) and placebo (N = 12).[17]

In a crossover study with treatment duration of 8 weeks, the adverse events reported between sevelamer capsules (N = 82) and calcium acetate (N = 82) treatment groups were similar (Table 4). The incidence of nausea, vomiting, diarrhea, and constipation was not statistically significant between groups. No serious adverse events related to medication occurred during either treatment.[28]

Table 4. Adverse Events from a Cross-Over Trial of Sevelamer Capsules versus Calcium Acetate for Eight Weeks of Treatment (N = 82) [28]

	Sevelamer	Ca Acetate
Adverse Event	N (%)	N (%)
Any	64 (78)	65 (79)
Body As a Whole	36 (44)	38 (46)
Headache	8 (10)	9 (11)
Infection	12 (15)	9 (11)
Pain	11 (13)	13 (16)
Cardiovascular	24 (29)	29 (35)
Hypertension	7 (9)	8 (10)
Hypotension	9 (11)	10 (12)
Thrombosis	8 (10)	5 (6)
Digestive	28 (34)	23 (28)
Diarrhea	13 (16)	8 (10)
Dyspepsia	9 (11)	3 (4)
Vomiting	10 (12)	4 (5)
Respiratory	8 (10)	18 (22)
Cough Increased	3 (4)	9 (11)

In a long-term, open-label extension trial, adverse events potentially related to sevelamer capsules were not dose related and included: nausea (7%), constipation (2%), diarrhea (4%), flatulence (4%), and dyspepsia (5%).[29]

Precautions/Contraindications

Contraindications:
Sevelamer is contraindicated in patients with hypophosphatemia or bowel obstruction. Sevelamer is contraindicated in patients known to be hypersensitive to sevelamer hydrochloride or any component of the formulation.[15]

Precautions:
The safety and efficacy of sevelamer in patients with dysphagia, swallowing disorders, severe gastrointestinal (GI) motility disorders, or major GI tract surgery have not been established. Consequently, caution should be exercised when sevelamer is used in patients with these GI disorders. Sevelamer may cause reductions in vitamin D, E, K, and folic acid absorption, thus requiring vitamin supplementation.[15]

Drug Interactions:
Sevelamer capsules were studied in human drug-drug interaction trials evaluating pharmacokinetic variability with digoxin, warfarin, enalapril, and metoprolol. Sevelamer did not alter the pharmacokinetic profile of a single dose of these drugs.[26,27] Due to sevelamer exhibiting bile acid-binding properties, it may bind to some drugs in the gastrointestinal tract and decrease their absorption. If changes in the bioavailability of a medication may have a significant clinical consequence on safety or efficacy, such as antiarrhythmic and antiseizure medications, these medications should taken 1 hour before or 3 hours after sevelamer, or a physician should consider monitoring serum levels of the drug. Patients taking antiarrhythmic or antiseizure medications were excluded from clinical trials, therefore, patients on these agents should take extra precautions before starting this medication.[15]

Clinical Trials

Citation[18]	**Chertow GM, Burke SK, Lazarus JM, et al. Poly(allylamine Hydrochloride (Renagel): A Noncalcemic phosphate binder for the treatment of hyperphosphatemia in chronic renal failure. *Am J Kidney Dis* 1997;29(1):66-71.**
Study Goals	To compare the safety and efficacy of Renagel Capsules with placebo in hemodialysis patients.
Methods	• **Study Design** ➢ Multicenter, double-blind, randomized, parallel group, placebo-controlled study. ➢ Duration of study was 8 weeks, following a 2-week baseline data collection, then a 2-week washout period, and a 2-week treatment period of Renagel (dose determined by calculating total daily dose of calcium in milligrams from the baseline phase and rounding to nearest 500mg) was compared to placebo. Patients returned to usual calcium- based phosphate binder in last 2 weeks. ➢ Primary outcome: Change in serum phosphorus concentration in relation to treatment with Renagel versus placebo ➢ n = 36 • **Data Analysis** ➢ Primary analysis based on intent-to-treat analysis, Student's t-test or ANOVA was performed on continuous variables and categorical variables were compared using Fisher's exact test. Linear regression analysis was performed using the change in serum phosphorus concentration as the dependent variable. Two-tailed probability values, ($P < 0.05$) were considered significant.
	• **Inclusion criteria** ➢ Men or women 18 years old or greater ➢ Three times per week hemodialysis for 3 months or longer ➢ On a stable dose of calcium-based phosphate binder for 1 month ➢ If using vitamin D, on a stable dose for 1 month ➢ Willing to avoid intentional changes in diet ➢ Patients willing to not take aluminum- or magnesium-based phosphate binders ➢ Women of childbearing potential willing to take effective contraceptive method • **Exclusion criteria** ➢ Patients with unstable medical condition, including poorly controlled diabetes mellitus, hypertension, dysphagia, swallowing disorders, severe gastrointestinal motility disorders, or major GI tract surgery ➢ Patients taking antiarrhythmic or antiseizure medications
Results	• Mean serum phosphorus significantly decreased by 1.4 mg/dL from baseline for Renagel capsules (7.0 mg/dL to 5.6 mg/dL), versus an increase by 0.26 mg/dL for placebo (7.3 mg/dL to 7.6 mg/dL); $P< 0.001$. • LDL cholesterol decreased significantly during Renagel capsule treatment (-17.6 mg/dL), but increased during placebo treatment (+7.3 mg/dL) ($P = 0.0026$) • Average dose of Renagel capsules was 3.5 grams per day • There were no significant differences between placebo and Renagel Capsules with regard to adverse events
Conclusions	Renagel capsules treatment was safe and well-tolerated, it significantly reduced serum phosphorus levels and was found to be as effective as calcium-based binders. Renagel also reduced total cholesterol and LDL cholesterol.
Critique	**Strengths:** Well designed trial, one of first to demonstrate clinical efficacy and safety of Renagel capsules in ESRD hemodialysis patients **Limitations:** Small patient population, short treatment period, claimed bioequivalency to calcium acetate or carbonate in a non-comparative trial

Citation[28]	**Bleyer AJ, Burke SK, Dillon M, 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(4): 694-701.**
Study Goals	To compare the safety and efficacy of Renagel capsules with calcium acetate in hemodialysis patients
Methods	• **Study Design** ➢ Multicenter, open-label, crossover study of Renagel capsules with calcium acetate ➢ After a 2-week washout period, 83 patients were treated with Renagel capsules or calcium acetate for 8 weeks. Patients were again washed out for 2 weeks and then received alternative medication for a further 8 weeks. ➢ Starting doses were either 2-4 Renagel capsules (465mg) or 1-3 tablets of calcium acetate (667mg) three times/day with meals, based on patients' initial degree of hyperphosphatemia. Dosage was increased by one capsule or one tablet per meal as needed to achieve a serum phosphorus between 2.5 and 5.5 mg/dL. Dosage of calcitriol throughout study remained the same • **Data Analysis** ➢ Wilcoxon signed-rank test assessed laboratory parameters, ANOVA was used to assess sequence, treatment, and sequence-by treatment interactions. McNemar's paired comparison test was used to assess differences between treatment groups for incidence of hypercalcemia.
Criteria	• **Inclusion criteria** ➢ Men and women 18 years of age or older ➢ Serum phosphorus > 6.0 mg/dL following a 2-week washout ➢ On three times/week hemodialysis for 3 months or longer ➢ On a stable dose of phosphate binder for 1 month ➢ If using vitamin D, on a stable dose for 1 month and willing to avoid intentional changes ➢ Patients willing to avoid intentional changes in diet • **Exclusion criteria** ➢ Patients with history of dyspepsia, swallowing disorders, severe gastrointestinal motility disorders, or major GI surgery. ➢ Patients taking antiarrhythmic or antiseizure medications
Results	• Mean change in serum phosphorus was similar for Renagel capsules (-2.0 mg/dL, P <0.0001) and calcium acetate (-2.0 mg/dL, P < 0.0001) • Incidence of hypercalcemia (serum calcium ≥ 11.0 mg/dL) was significantly lower during Renagel capsules treatment (5%) than during calcium acetate treatment (22%) (P< 0.05) • Serum total and LDL cholesterol decreased significantly during Renagel capsules [-26.5 mg/dL (-15%) and –25.3 mg/dL (-24%), respectively, (P < 0.0001)] but remained unchanged for calcium acetate treatment, HDL and TG levels were unchanged in both treatment groups. • Mean daily dose at end of treatment for Renagel capsules (4.9 g/d) was similar to calcium acetate (5.0 g/d). • Both medications were well tolerated without significant adverse effects. No significant differences existed for the most common adverse events of Renagel and calcium acetate: diarrhea (16% and 10%, respectively), infection (15% and 11%, respectively), and pain (13% and 16%, respectively). • Intact PTH levels decreased significantly with both treatments, but more so with calcium acetate (-100.6 pg/ml) vs (-48.2 pg/ml), P = 0.17
Conclusions	Reduction in serum phosphorus was similar and statistically significant for Renagel capsules and calcium acetate. Renagel capsules were safe and well-tolerated. The incidence of hypercalcemia was lower with Renagel capsules treatment compared to calcium acetate treatment. Renagel significantly reduced serum total and LDL cholesterol with Renagel treatment.

Citation[14]	**Slatoplosky EA, Burke SK, Dillon MA, and the Renagel Study Group. Renagel, a nonabsorbed calcium- and aluminum-free phosphate binder, lowers serum phosphorus and parathyroid hormone. *Kidney International* 1999;55:299-307**
Study Goals	To investigate the safety and efficacy of Renagel capsules in hemodialysis patients
Methods	• **Study Design** ➢ Multicenter, open-label, dose titration study of Renagel capsules ➢ After a 2-week washout period, Renagel treatment was started at doses of two, three, or four 440mg capsules three times a day with meals for 8 weeks. Renagel doses could increase by one capsule per meal every two weeks as necessary to achieve serum phosphorus control, n = 172 ➢ Primary outcome: Efficacy of Renagel in lowering serum phosphorus levels ➢ Secondary Outcomes: Renagel effects on intact parathyroid hormone (iPTH), serum lipids, and calcium levels • **Data Analysis** ➢ All statistical tests were based on two-tailed hypothesis tests, with significance level of P< 0.05. Wilcoxon signed rank tests assessed changes in dietary intake and serum concentrations. Linear regression model was used to identify factors associated with changes in serum phosphorus. Spearman rank correlation was used to examine relationship between the change in serum phosphorus, calcium, and iPTH. Chi-squared tests were used to test Renagel dose level group differences for adverse effects
Criteria	• **Inclusion criteria** ➢ Male or female hemodialysis patients 18 years of age or older ➢ Hemodialysis minimum of three months with three times/week ➢ Serum phosphorus > 6.0 mg/dL following a 2-week washout ➢ On a stable dose of phosphate binder for 1 month ➢ If using vitamin D, on a stable dose for 1 month and willing to avoid intentional changes. • **Exclusion criteria** ➢ Patients with history of dysphagia, swallowing disorders, severe gastrointestinal motility disorders, or major GI tract surgery ➢ Patients currently taking antiarrhythmic or antiseizure medications
Results	• Serum phosphorus decreased significantly from baseline to final (-2.5 mg/dL from 9.1 md/gL, P < 0.0001) • Calcium x phosphorus product declined significantly from 82.1 mg/dL at baseline to 61.4 mg/dL (P<0.0001) • Median serum intact parathyroid hormone decreased significantly from baseline to final (-63 pg/ml from 316 pg/ml, P< 0.0001) • Serum calcium was in the normal range throughout the treatment period • LDL cholesterol decreased significantly from baseline to final (-18.2%, P< 0.0001). Triglycerides and HDL cholesterol did not change. • Average actual dose at the end of treatment was 5.4g of Renagel capsules per day • Most common adverse events related to Renagel were diarrhea (6%), dyspepsia (6%), and vomiting (5%)
Conclusions	Renagel capsules were a safe and well-tolerated treatment that significantly reduced serum phosphorus, intact parathyroid hormone, and serum total and LDL cholesterol levels.
Critique	• **Strengths:** First trial to show statistical significance in lowering iPTH in patients taking Vitamin D with Renagel treatment, larger patient population and longer study period than previous trials • **Limitations:** Study design was not placebo controlled, double blinded; non-comparative trial

Citation[29]	**Chertow GM, Burke SK, Dillon MA, Slatopolsky E, for the Renagel Study Group. Long-term effects of sevelamer hydrochloride on the calcium x phosphate product and lipid profile of hemodialysis patients. *Neph Dialysis Trans* 1999 14(12):2907-2914.**
Study Goals	To investigate the long-term safety and efficacy of Renagel capsules in hemodialysis patients.
Methods	• **Study Design** ➢ Multicenter, open-label, dose titration study of Renagel capsules ➢ Following a 2-week washout period, patients were treated with Renagel for 44 weeks, n = 192 ➢ Renagel capsules starting dose was determined based on the patient's previous Renagel capsule experience, the patient's dietary intake, and the investigator's clinical judgement. ➢ Drug-related changes in concentrations of serum phosphorus, calcium, calcium x phosphate product, parathyroid hormone, and LDL and HDL cholesterol concentrations were major areas of interest. • **Data Analysis** ➢ Continuous variables were compared with Student's *t*-test, the Wilcoxon signed rank test, or the Kruskal-Wallis test, where appropriate. Categorical variables were compared with Fisher's Exact test. Dose-response was tested by linear regression (laboratory parameter of interest as dependent variable, and sevelamer dose as continuous independent variable)
Criteria	• **Inclusion criteria** ➢ 18 years of age or above ➢ Three times/week hemodialysis for at least 3 months, ➢ Regular administration of aluminum- and/or calcium-based phosphate binders with or without Vitamin D metabolite replacement therapy stable on doses for at least 1 month. ➢ Prior participation in a Renagel capsule trial which required a serum phosphorus >6.0mg/dL following a 2-week washout • **Exclusion criteria** ➢ Serious gastrointestinal disease (including dysphagia, vomiting, motility disorder, major GI surgery, irregular bowel function), ethanol or drug dependence or abuse, active malignancy, HIV infection, vasculitis, or poorly controlled diabetes mellitus or hypertension
Results	• Serum phosphorus decreased significantly from baseline (-2.2mg/dL from 8.7 mg/dL, P<0.0001) • Calcium x phosphate product decreased significantly from baseline to final (-18.1mg/dL from 78.4mg/dL, P< 0.0001) • Serum total and LDL cholesterol decreased significantly from baseline to final [-27.9 mg/dL (-15%) and –31.5 mg/dL (-29%) respectively, P < 0.0001]. The greatest reduction in LDL was found in patients with LDL levels >160mg/dL at baseline. • HDL cholesterol increased significantly from baseline (0.15± 0.29 mmol/L; P<0.0001), an average of 18% over baseline. • Average dose of Renagel capsules was 5.3 grams/day • Adverse events possibly related to Renagel capsules were not dose related and included: nausea (7%), constipation (2%), diarrhea (4%), flatulence (4%), and dyspepsia (5%).
Conclusions	Extended use of Renagel capsules significantly reduced serum phosphorus levels, serum calcium x phosphorus product, and total and LDL cholesterol. Renagel capsules were safe and well-tolerated
Critique	• **Strengths:** First trial evaluating extended-use of Renagel capsule, largest patient population compared to earlier trials • **Limitations:** Design was not placebo-controlled, double blinded, and it did not compare safety and efficacy to the competitive agent calcium acetate. No restrictions enforced on administration of vitamin D metabolites, supplemental calcium, or other conventional or alternative drug therapies during trial.

Acquisition Costs/ Cost Analysis

Drug	Dose	Price/Unit	Cost/Day/pt ($)	Cost/Year/pt ($)	Annual Cost per 3500 patients *
Renagel 800mg TAB	1-2 tablets TID	$ 0.712	$2.14 – $4.27	$781 - $1559	$2,733,500 - $5,456,500
Renagel 403mg CAP	2-4 capsules TID	$ 0.353	$2.12 – $4.24	$774 - $1548	$2,709,000 – $5,418,000
Renagel 400mgTAB	2-4 tablets TID	$0.359	$2.15 – $4.31	$786 - $1573	$2,751,000 - $5,505,500
Calcium Acetate 667mg TAB	1-3 tablets TID	$0.054	$0.16 - $0.49	$59 – $177	$206,955 - $620,865

∗ Estimated number of ESRD patients who may benefit from sevelamer per year within VHA

	Sevelamer HCL 400mg TAB	Sevelamer HCL 403mg CAP	Sevelamer HCL 800mg TAB	Calcium Acetate 667mg TAB
Total Cost January-June 2002	$139,343	$344,025	$1,366,478	$3,260

Sevelamer Dose	Total Rx 2000	Total Quantity 2000	Quantity/ Rx 2000	30d Rx 2001	Total Quantity 2001	Quantity/ Rx 2001	30d Rx 2002*	Total Quantity 2002*	Quantity/ Rx 2002*
403 mg	5375	1,814,551	338	10644	2,999,149	282	3832	997,477	260
400mg				2995	915,624	306	1530	395,544	258
800mg	54	14,009	260	6350	1,195,661	188	8626	1,936,582	224

* January – June 2002

Conclusions

Sevelamer hydrochloride is a well-tolerated and effective alternative for the management of hyperphosphatemia in ESRD patients on hemodialysis. Patients who may benefit from sevelamer are those who are at risk of cardiac and other soft tissue calcifications due to elevated serum phosphorus, elevated calcium x phosphorus product, and excessive calcium intake. Sevelamer has also been shown to significantly reduce total and LDL cholesterol in ESRD patients. It is not known whether the reduction in calcium score with sevelamer compared to calcium-based binders translates into a reduction in long-term outcomes.

Recommendations

Sevelamer hydrochloride has been shown to be a safe, effective, and well-tolerated alternative to traditional calcium-based phosphate binders. Studies have shown sevelamer to effectively reduce serum phosphorus and calcium x phosphorus products without significant hypercalcemia or other adverse events. With increased concerns of hypercalcemia, constipation, and soft tissue and cardiac calcifications associated with traditional therapy, calcium-based binders and vitamin D for calcium and phosphorus management, sevelamer is an alternative therapy to reduce serum phosphorus without the unwanted side effects in hemodialysis patients. Whether the potential benefits of sevelamer over calcium-based binders translates into long-term outcomes remains to be determined. It is recommended that sevelamer remain non-formulary, restricted to Nephrology and national criteria for use (refer to criteria listed on the following page).

Sevelamer Hydrochloride (Renagel®) Criteria for Nonformulary Use in VA Patients with ESRD on Dialysis

Sevelamer is restricted to Nephrology Service.

The following recommendations are provided for the use of sevelamer for the treatment of hyperphosphatemia in patients with end stage renal disease (ESRD) on dialysis (hemodialysis or peritoneal dialysis). Sevelamer is NOT to be used in patients who are not on dialysis.

Patients must have a diagnosis of ESRD and are receiving renal replacement therapy (i.e., hemodialysis or peritoneal dialysis) AND one or more of the following:

- Calcium x phosphorus product > 55 mg^2/dl^2 despite dietary restriction of phosphate to < 1gm/d AND calcium (carbonate or acetate) [a]
- Serum phosphorus > 7 mg/dl despite dietary restriction of phosphate to < 1gm/d AND calcium (carbonate or acetate)
- Total serum calcium (corrected for serum albumin) [b] $\geq$ 10.5mg/dl (or maximum per lab/facility) on conventional treatment with calcium carbonate or calcium acetate phosphate binding therapy [a] and despite discontinuation of vitamin D preparations
- Parathyroid hormone level < 100 pcg/ml with normal or elevated serum calcium (for patients with adynamic bone disease)

[a] An aluminum containing phosphate binder should NOT be used for long-term management of hyperphosphatemia due to potential toxicity. In addition, use of 2.5mEq/L calcium dialysate should be part of therapy to reduce hypercalcemia.
[b] Calculation for corrected serum calcium: normal serum albumin (4gm/dl) – most recent serum albumin = X; 0.8X = Y
Measured serum calcium + Y = corrected serum calcium
Ex. Calcium 9.9mg/dl; albumin 3.2gm/dl
4 – 3.2 = 0.8; 0.8 X 0.8 = 0.64
9.9 + 0.64 = 10.54 (10.5mg/dl is the corrected serum calcium)

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