Criteria for Nonformulary Use of Sevelamer Hydrochloride in VA Patients with Chronic Kidney Disease and Kidney Failure on Dialysis

VA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel

The following recommendations are based on current medical evidence and expert opinion from clinicians. The content of the document is dynamic and will be revised as new clinical data becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient. The manufacturer's labeling should be consulted for detailed information when prescribing sevelamer.

Background

Patients with chronic kidney disease (CKD) with kidney failure 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.[1,2] 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.[3] Recent studies have demonstrated an association between excessive calcium intake and coronary artery calcification in patients with CKD with kidney failure.[4,5]

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 (although use is limited by reports of aluminum toxicity such as osteomalacia, myopathy, anemia, and dementia), and dialysis.[6] Sevelamer hydrochloride (Renagel®), is a nonabsorbed calcium-free, aluminum-free phosphate binder that has been shown to decrease serum phosphorus levels in patients with CKD who are on hemodialysis. The safety and efficacy of sevelamer hydrochloride in CKD patients who are not on hemodialysis has not been studied.[7-9] Sevelamer has also been compared to calcium-based phosphate binders and found to have a significant difference in the absolute change in calcification score from baseline as measured in the coronary arteries and in the aorta,[10] although whether or not this translates into a difference in outcomes requires further study.

The VHA Clinical Practice Guidelines for the Management of Chronic Kidney Disease and Pre-End Stage Renal Disease in the Primary Care Setting states that sevelamer may be used in patients with hypercalcemia for lowering phosphate in patients with CKD, but the high cost (and recent introduction) will probably limit its use to Nephrology Service.[11] More recent recommendations of the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K/DOQI) Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease state that in patients with CKD with kidney failure (stage 5), that both calcium-based phosphate binders and nonabsorbed calcium-free, aluminum-free phosphate binders (e.g., sevelamer) are effective in lowering serum phosphorus levels (based on medical evidence), and either may be used as primary therapy (recommendation based on opinion).[12]

Recommendations[1,2,4,12]

Sevelamer is restricted to Nephrology Service. Sevelamer is NOT to be used in patients who are not on dialysis.

Criteria for Nonformulary Use of Sevelamer in CKD with Kidney Failure (Stage 5) on Dialysis
Patients must have a diagnosis of Stage 5 CKD (defined as kidney failure with GFR < 15mL/min/1.72m^2 or dialysis) and are receiving kidney replacement therapy (i.e., hemodialysis or peritoneal dialysis) AND one or more of the following:
↑ Serum phosphorus > 6.5mg/dl despite dietary restriction of phosphate to < 1gm/d AND calcium based phosphate binders[a]
↑ Total serum calcium (corrected for serum albumin)[b] ≥ 10.2mg/dl (or maximum per lab/facility) on conventional treatment with calcium based phosphate binding therapy[a] and despite discontinuation of vitamin D preparations for at least 1 month
↑ Intact plasma parathyroid hormone (PTH) level < 2 times the upper limit of normal for PTH assay with normal or elevated serum calcium
↑ Calcium x phosphorus product > 55mg^2/dl^2 despite dietary restriction of phosphate to < 1gm/d AND calcium based phosphate binders[a]

[a] An aluminum containing phosphate binder should NOT be used for long-term management of hyperphosphatemia due to potential toxicity. K/DOQI Guideline recommendations are to limit elemental calcium intake from phosphate binders to < 1500mg/d (based on Opinion; corresponds to USPSTF Quality of Evidence Level III: refer to Harris RP, Helfand M, Woolf SH, et al. for the Methods Work Group, Third U.S. Preventive Services Task Force. Current methods of the U.S. Preventive Services Task Force. A review of the process. Am J Prev Med 2001;20(3S):21-35.) In addition, use of 2.5mEq/L calcium dialysate should be part of therapy to reduce hypercalcemia.

[b] Calculation for corrected total serum calcium=total calcium + 0.8 (4 - serum albumin)
[4gm/dl (normal serum albumin) – most recent serum albumin]
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)

Adverse Drug Events

Adverse Drug Event[a]	Sevelamer HCl	Ca Acetate (%)
Any	78%	79%
Body As a Whole	44%	46%
Headache	10%	11%
Infection	15%	11%
Pain	13%	16%
Cardiovascular	29%	35%
Hypertension	9%	10%
Hypotension	11%	12%
Thrombosis	10%	6%
Digestive	34%	28%
Diarrhea	16%	10%
Dyspepsia	11%	4%
Vomiting	12%	5%
Respiratory	10%	22%
Cough Increased	4%	11%

[a] Adverse events from a cross-over trial of sevelamer capsules vs. calcium acetate (Ca Acetate) for eight weeks of treatment (N = 82)[13]

Precautions[14]

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.

Contraindications

- Hypophosphatemia or bowel obstruction
- Known hypersensitivity to sevelamer or any component of the formulation

Drug Interactions

- Due to sevelamer exhibiting bile acid-binding properties, patients on medications where changes in the bioavailability may have a significant clinical consequence on safety or efficacy (e.g., antiarrhythmic and antiseizure medications), should be instructed to take these medications 1 hour before or 3 hours after sevelamer, or a physician should consider monitoring serum levels of the drug

Dosing[14]

Starting Dose of Sevelamer for Patients Not Taking a Phosphate Binder

Serum Phosphorus	Sevelamer 800mg[a]	Sevelamer 400mg[a]
>6.0 and < 7.5 mg/dL	1 tablet three times daily	2 tablets three times daily
>7.5 and <9.0 mg/dL	2 tablets three times daily	3 tablets three times daily
>9.0 mg/dL	2 tablets three times daily	4 tablets three times daily

[a] Should be taken with meals

Starting Dose for Patients Switching From Calcium Acetate to Sevelamer [a]

Ca Acetate 667mg [b]	Sevelamer 800mg [b]	Sevelamer 400mg [b]
1 tablet	1 tablet	2 tablets
2 tablets	2 tablets	3 tablets
3 tablets	3 tablets	5 tablets

[a] Clinical trials involving 84 CKD patients with kidney failure on hemodialysis showed similar reductions in serum phosphorus with equivalent doses (mg for mg) of sevelamer capsules and calcium acetate
[b] Should be taken with meals

Dose Titration

Doses should be adjusted gradually according to serum phosphorus concentrations by increasing or decreasing one tablet per meal every two weeks. The proper dose is that which lowers serum phosphorus to 3.5-5.5 mg/dL and calcium-phosphorus product <55 mg^2/dL^2 according to the 2003 K/DOQI Clinical Practice Guidelines. The average dose of sevelamer used in a comparison trial with calcium-based binders was 6.5 $\pm$ 2.9 gm/day (~ eight 800 mg tablets).[10]

Cost Comparison

Drug	Dose	Price/Unit	Daily Cost/Patient	Annual Cost/Patient
Sevelamer 400mg tablet	2-6 tablets TID	$0.3736	$2.24-$6.73	$807-$2,421
Sevelamer 800mgtablet	1-3 tablets TID	$0.7482	$2.25-$6.73	$808-$2,424
Ca Acetate 667mg tablet[a]	1-3 tablets TID	$0.0868	$0.26-$0.78	$94-$281
Ca Carbonate 650mg tablet[b]	1-2 tablets BID-TID	$0.0055	0.01-0.03	$3.60-$10.80

[a] 253 mg elemental calcium per gram
[b] 400mg elemental calcium per gram

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Also refer to the National PBM Drug Monograph for sevelamer at www.vapbm.org or http://vaww.pbm.med.va.gov

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