

**Phosphate Binders (Non-Calcium, Non-Aluminum)**  
**Lanthanum Carbonate, Sevelamer Carbonate, Ferric Citrate, Sucroferric Oxyhydroxide**  
**For the Management of Hyperphosphatemia in Chronic Kidney Disease**  
**Recommendations for Use**  
**May 2016**  
**VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives**

**Background:**

The Kidney Disease: Improving Global Outcomes (KDIGO) Chronic Kidney Disease-Mineral and Bone Disorder guidelines (2009; update in progress) suggest maintaining serum phosphorus in the normal range for patients with chronic kidney disease (CKD) stages 3 to 5 (Strength of Recommendation: Weak; Quality of Evidence: Low), and lowering elevated phosphorus toward the normal range in patients with CKD stage 5 on dialysis (Strength of Recommendation: Weak; Quality of Evidence: Low). Data remain inconclusive as to whether there is a difference in long-term clinical outcome benefit among the phosphate binders (i.e., calcium based phosphate binders compared to non-calcium based phosphate binders). Until additional data are available, a calcium based phosphate binder is recommended as initial therapy in patients with hyperphosphatemia and CKD (with consideration for a non-calcium based phosphate binder as noted in the following treatment algorithm). (National Institute for Health and Clinical Excellence [NICE] 2013, evidence update 2014). The comparison chart and treatment algorithm below are provided as guidance in the selection of a non-calcium, non-aluminum phosphate binder, as indicated.

	<b>Lanthanum carbonate</b>	<b>Sevelamer carbonate</b>	<b>Ferric citrate</b>	<b>Sucroferric oxyhydroxide</b>
<b>Formulary Status</b>	VA National Formulary <sup>a</sup> (tablets only)	VA National Formulary <sup>a</sup> (tablets only)	Non-formulary	Non-formulary
<b>FDA Indication</b>	Reduce phosphorus in ESRD	Control phosphorus in CKD on dialysis	Control phosphorus in CKD on dialysis	Control phosphorus in CKD on dialysis
<b>Product Strength and Availability</b>	250 mg, 500 mg, 750 mg, 1000 mg chewable <sup>b</sup> tablets 750 mg, 1000 mg powder packets <sup>a,c</sup>	800mg tablets 800 mg, 2400 mg powder packets <sup>a,d</sup>	210 mg tablets	500 mg chewable <sup>b</sup> tablets
<b>Dose</b>	1500 to 3000 mg/day divided 3 times daily <sup>e</sup> Initial dose 500 mg 3 times daily; increased (e.g., by 750 mg every 2 to 3 weeks) until serum phosphorus goal achieved Usual maintenance dose (to reduce phosphorus < 6.0 mg/dl in clinical trials) 1500 mg to 3000 mg daily (maximum dose studied 4500 mg daily)	2400 to 7200 mg/day divided 3 times daily <sup>e</sup> Initial dose 800 mg to 1600 mg 3 times daily; increase by 800 mg 3 times daily every 2 weeks, based on response In clinical trials, mean doses 5500 mg and 6000 mg per day reduced phosphorus to 4.8 and 4.6 mg/dl, respectively; average daily dose 7200 mg/day (9 tablets); maximum dose studied 14000 mg daily	1260 to 2520 mg/day divided 3 times daily <sup>e</sup> Initial dose 210 mg (ferric iron; equivalent to 1 gm ferric citrate) 2 tablets 3 times daily; adjust dose by 1 to 2 tablets (at interval of 1 week or more) to maintain phosphorus at target levels, up to a maximum 12 tablets daily	1500 to 3000 mg/day divided 3 times daily <sup>e</sup> Initial dose 500 mg 3 times daily (each tablet contains 500 mg iron; 2,500 mg sucroferric oxyhydroxide); titrate (by 1 tablet per day, as often as on a weekly basis) to achieve target phosphorus; maximum 3000 mg daily (total 6 tablets per day)
<b>Tablet burden</b>	3 tablets/day (or 2 to 3 packets/day)	3 to 9 tablets/day (or three to nine 800 mg packets; or one to three 2400 mg packets/day) Max dose studied equivalent to 17.5 tablets/day, or 5.8 of the 2400 mg packets/day	6 to 12 tablets/day Ferric citrate (8.0 tablets/day) similar to calcium acetate (7.7 tablets/day) and sevelamer carbonate (9.0 tablets/day)	3 to 6 tablets/day Sucroferric oxyhydroxide (mean ~ 3 tablets/day) non-inferior to sevelamer carbonate (~ 8 tablets/day)
<b>Off-label use</b>	CKD not on dialysis	CKD not on dialysis	CKD not on dialysis <sup>f</sup> Increased ferritin and TSAT vs. control; decreased use IV iron and ESAs	CKD not on dialysis <sup>f</sup>

Table Continued	Lanthanum carbonate	Sevelamer carbonate	Ferric citrate	Sucroferric oxyhydroxide
<b>Contraindications</b>	Bowel obstruction, including ileus and fecal impaction	Bowel obstruction	Iron overload syndromes (e.g., hemochromatosis)	None
<b>Common Adverse Effects</b>	Nausea, vomiting, abdominal pain	Vomiting, nausea, diarrhea, dyspepsia, abdominal pain, flatulence, constipation	Diarrhea, nausea, constipation, vomiting, cough, dark stools (due to iron content)	Diarrhea, nausea, dark stools (due to iron content)
<b>Drug interactions</b>	<p>Medications where reduction in bioavailability may result in significant impact on safety or efficacy should consider separation of the two medications (timing will depend on the absorption of the interacting drug); consider monitoring clinical response or blood levels of interacting medication, if applicable</p> <p>Medications that interact with antacids should not be administered within 2 hours of lanthanum carbonate</p> <p>Administer oral quinolones at least 1 hour before or 4 hours after lanthanum carbonate</p> <p>Decreased bioavailability of levothyroxine (levothyroxine should be taken at least 2 hours before or 2 hours after lanthanum carbonate; monitor TSH in patients taking lanthanum carbonate and thyroid hormone replacement therapy)</p>	<p>Medications where reduction in bioavailability (e.g., cyclosporine, tacrolimus, levothyroxine) may result in significant impact on safety or efficacy should consider separation of the two medications (timing will depend on the absorption of the interacting drug); consider monitoring clinical response or blood levels of interacting medication, as applicable</p> <p>It is recommended that ciprofloxacin be administered 2 hours before or 6 hours after sevelamer; mycophenolate mofetil should be taken at least 2 hours before sevelamer</p>	<p>Take doxycycline at least 1 hour before ferric citrate; take ciprofloxacin at least 2 hours before or after ferric citrate</p> <p>Consider separating other medications where an effect on bioavailability may alter the safety or efficacy of the drug (e.g., separate oral administration of iron salts and levothyroxine by at least 4 hours); monitor clinical response or drug levels of medications with a narrow therapeutic range</p>	<p>Take doxycycline at least 1 hour before sucroferric oxyhydroxide</p> <p>Consider separating other medications where an effect on bioavailability may alter the safety or efficacy of the drug</p> <p>Levothyroxine should not be prescribed with sucroferric oxyhydroxide</p>
<b>Pregnancy and Lactation</b>	<p><b>Pregnancy Category C:</b> not recommended during pregnancy</p> <p>No adequate well-controlled studies in pregnant women</p> <p>Data not available on effect of lanthanum carbonate on absorption of vitamins and other nutrients</p> <p>Studies of doses 5 times MRHD in pregnant rabbits was associated with increased post-implantation loss, decreased fetal weight, and delayed fetal ossification</p> <p><b>Lactation:</b> It is not known if lanthanum carbonate is excreted in human milk; consider the possibility of infant exposure in nursing females</p>	<p><b>Pregnancy Category C:</b> should only be used during pregnancy if potential benefit justifies potential risk to fetus</p> <p>No adequate well-controlled studies in pregnant women</p> <p>Data not available on effect of sevelamer on absorption of vitamins and other nutrients in pregnant women</p> <p>Pregnant rats given sevelamer (equivalent to ~maximum clinical trial dose) during organogenesis was associated with reduced or irregular ossification of fetal bones; pregnant rabbits given sevelamer (approximately twice maximum clinical trial dose) during organogenesis was associated with an increase of early resorptions</p> <p><b>Lactation:</b> Sevelamer is not absorbed; however, consider potential for reduced</p>	<p><b>Pregnancy Category B:</b> no adequate, well-controlled studies in pregnant women</p> <p>Data not available on effect of ferric citrate on absorption of vitamins and other nutrients</p> <p>Iron overdose in pregnant women may increase risk for spontaneous abortion, gestational diabetes and fetal malformation</p> <p>Animal reproduction studies have not been conducted</p> <p><b>Lactation:</b> Iron has been shown to be transferred to breast milk in rats; consider the possibility of exposure infant exposure to iron in nursing females taking ferric citrate</p>	<p><b>Pregnancy Category B:</b> no adequate, well-controlled studies in pregnant women</p> <p>Reproduction studies in rats up to 16 times MRHD, and in rabbits up to 4 times MRHD, did not show evidence of impaired fertility or harm to the fetus</p> <p>In pregnant rats, doses up to 16 times MRHD was associated with increase in post-implantation loss</p> <p><b>Lactation:</b> Absorption of iron from sucroferric oxyhydroxide is minimal; excretion of the drug in breast milk is unlikely</p>

		absorption of some vitamins in nursing females		
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CKD=chronic kidney disease; ESAs=erythropoiesis-stimulating agents; ESRD=end-stage renal disease; IV=intravenous; MRHD= maximum recommended daily human dose; TSAT=transferrin saturation; TSH=thyroid stimulating hormone

Refer to the respective product labeling for detailed prescribing information and additional recommendations on warnings/precautions, adverse events, drug interactions, and monitoring

<sup>a</sup> Lanthanum carbonate powder available non-formulary; sevelamer hydrochloride and sevelamer carbonate powder available non-formulary

<sup>b</sup> Chew thoroughly (tablets may be crushed to assist in chewing) prior to swallowing; tablets should not be swallowed intact

<sup>c</sup> Sprinkle lanthanum carbonate powder on a small quantity of applesauce or other similar food and consume immediately

<sup>d</sup> Contents of powder packet should be mixed with recommended amount of water (e.g., minimum 30 ml for 0.8 gm packet, 60 ml for 2.4 gm packet) to suspend medication (will not dissolve); consume entire contents within 30 minutes (or resuspend immediately prior to consumption)

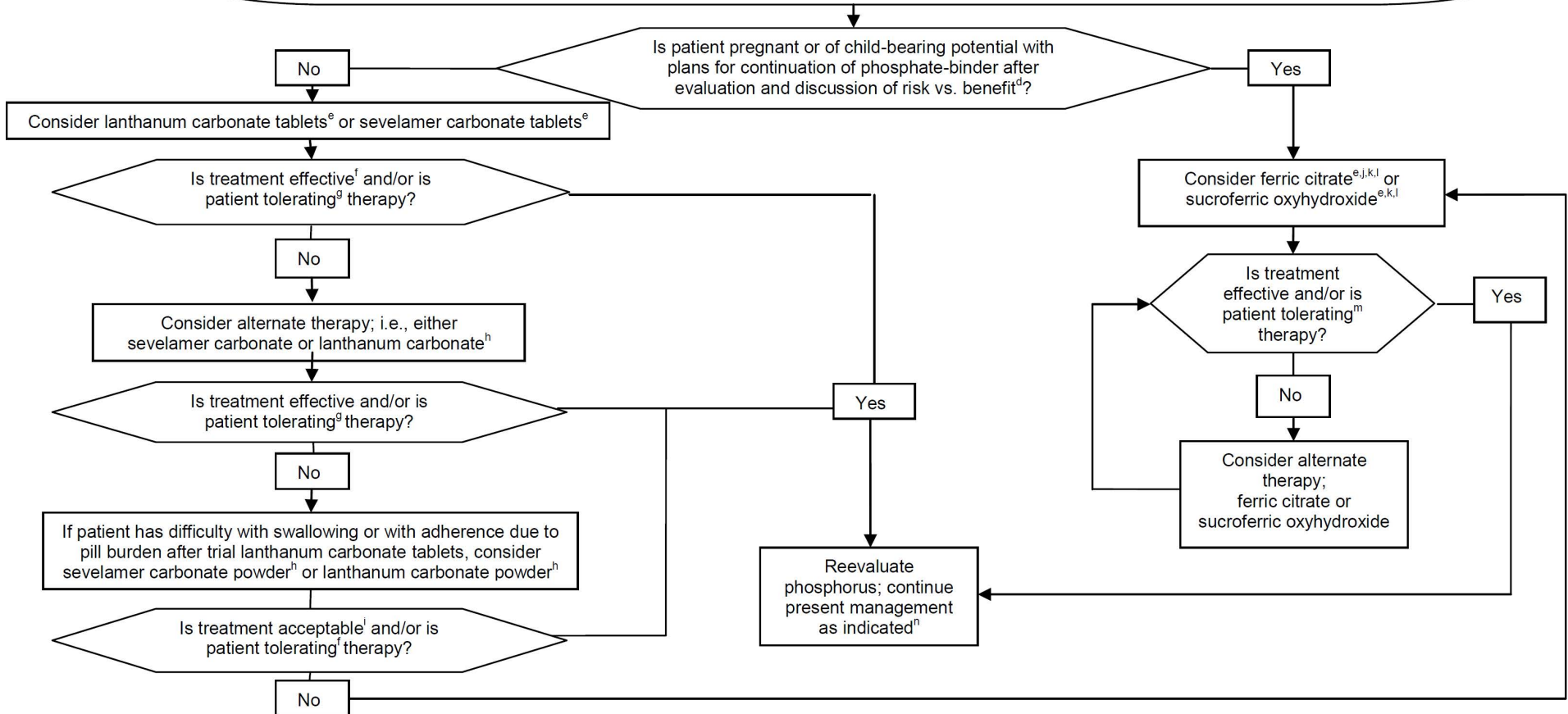
<sup>e</sup> Recommended to be administered with meals

<sup>f</sup> Limited data

# Treatment Algorithm for Phosphate Binders (Non-calcium, Non-aluminum) in Patients with Hyperphosphatemia and CKD

Patient with Stage 3 to 5 CKD with or without KRT (HD or PD) and documented hyperphosphatemia AND one or more of the following<sup>a</sup>:

- persistently elevated serum phosphorus despite dietary restriction of phosphate and adherence to calcium-based phosphate binders<sup>b</sup>;
- intolerance to (e.g., unmanageable significant adverse event) a calcium based phosphate binder;
- elevated total serum calcium (corrected for serum albumin)<sup>c</sup> on conventional treatment with calcium based phosphate binding therapy<sup>b</sup> and despite adjustment of vitamin D preparations to lowest effective dose;
- low iPTH level with normal or elevated serum calcium associated with adynamic bone disease



CKD=chronic kidney disease; ESAs=erythropoiesis-stimulating agents; HD=hemodialysis; iPTH=intact parathyroid hormone; KRT=kidney replacement therapy; PD=peritoneal dialysis; VANF=VA National Formulary

<sup>a</sup> Conflicting data are available as to the potential for reduced progression of vascular calcification with a non-calcium phosphate binder (sevelamer hydrochloride) compared to a calcium based phosphate binder (KDIGO 2009; Cochrane Review 2011). According to a meta-analysis, it has been suggested that use of a non-calcium phosphate binder may reduce mortality compared to calcium based phosphate binders (Jamal 2013). A review of this meta-analysis was conducted and found to have several limitations (DARE 2013; NICE 2014). Additional data are needed in order to be able to make a recommendation on preference for use of a non-calcium based vs. calcium based phosphate binder in patients with CKD, especially those with vascular calcification; therefore, use should be determined on a case by case basis in these patients.

<sup>b</sup> The most frequently used calcium-based phosphate binders that are listed on VANF include calcium acetate and calcium carbonate. Recommendations have been to limit elemental calcium intake from phosphate binders to < 1500 mg/d, with the total daily intake (including dietary calcium) of elemental calcium not to exceed 2000 mg. In general, it is recommended that 2.5 mEq/l (1.25 mmol/l) calcium dialysate for patients on hemodialysis, and 2.5 to 3.0 mEq/l (1.25 to 1.5 mmol/l) for peritoneal dialysis should be part of therapy to reduce hypercalcemia; however, this should be based on individual patient requirements. An aluminum containing phosphate binder should NOT be used for long-term management of hyperphosphatemia due to potential toxicity.

<sup>c</sup> Calculation for corrected total serum calcium=total calcium + 0.8 (4 - serum albumin). The normal serum albumin of 4.0gm/dl is based on measurements using bromocresol green. If the bromocresol purple method is used, the normal serum albumin should be adjusted accordingly (e.g., 3.5gm/dl). Local laboratory should be contacted to determine if this correction should be applied to the current result.

[4 gm/dl (normal serum albumin) – most recent serum albumin]

Ex. Calcium 9.9 mg/dl; albumin 3.2 gm/dl

[4 – 3.2] = 0.8; 0.8 X 0.8 = 0.64

9.9 + 0.64 = 10.54 (10.54 mg/dl is the corrected serum calcium)

<sup>d</sup> Patients should be provided contraceptive counseling and education on potential risk vs. benefit of taking these agents if they were to become pregnant.

<sup>e</sup> Restricted to Nephrology for the initial prescription (refer to comparison table for treatment considerations); if deemed appropriate, local P&T Committees may approve selected providers to initiate or renew prescriptions.

<sup>f</sup> Effective on maximally tolerated dose; limited data on sevelamer and calcium-based phosphate binder used in combination, consider on a case by case basis only.

<sup>g</sup> Intolerance including an adverse event or difficulty with adherence due to dosage formulation or pill burden.

<sup>h</sup> If patient is having difficulty with adherence due to dosage formulation or pill burden, lanthanum carbonate chewable tablet available for ease in swallowing (or tablets may be crushed to assist in chewing), may also offer reduced pill burden depending on the dose required to attain treatment goal; if continued intolerance or inefficacy after trial lanthanum carbonate tablets, consider non-formulary sevelamer carbonate powder if patient has difficulty with swallowing or with adherence due to pill burden (taking into consideration amount of fluid required per dose of sevelamer powder i.e., minimum 30 ml for 0.8 gm packet, 60 ml for 2.4 gm packet); lanthanum carbonate powder also available non-formulary for use in these patients, as indicated.

<sup>i</sup> Consider referral to dietitian, evaluate adherence to therapy with lanthanum carbonate or sevelamer carbonate; iron-based phosphate binders anticipated to provide comparable efficacy.

<sup>j</sup> The role of ferric citrate for its effects on iron parameters and potential impact on utilization of iron replacement therapy and/or ESAs in patients with CKD on dialysis being treated for elevated phosphorus has yet to be established; until additional data are available, use of ferric citrate in this patient population should only be done under careful consideration of the risk vs. benefit on a case by case basis.

<sup>k</sup> Adequate data on the long-term safety and efficacy of ferric citrate or sucroferric oxyhydroxide in patients with CKD not on dialysis are not available at this time to determine its place in therapy in these patients and should only be done under careful consideration of the risk vs. benefit on a case by case basis.

<sup>l</sup> Refer to table for treatment considerations; if either ferric citrate or sucroferric oxyhydroxide would be an acceptable option, consider initiation with the most cost-effective therapy.

<sup>m</sup> Intolerance including an adverse event or difficulty with adherence due to dosage formulation or pill burden (e.g., sucroferric oxyhydroxide chewable tablet dosage form for ease in swallowing, may also offer reduced pill burden depending on the dose required to attain treatment goal); if continued intolerance or inefficacy, consider sevelamer carbonate after considering risk vs. benefit in Pregnancy.

<sup>n</sup> Recommendations for discontinuation or decrease in dose:

- If the patient does not respond adequately to an average/usual maintenance dose of phosphate binder, reevaluate adherence to the medication regimen and to dietary restrictions; consider referral to dietitian and reinforce importance of medication adherence
- If patient is deemed adherent and experiences no or minimal response to most recent increase in dose (up to maximum studied doses), recommend decrease to lowest effective dose
- Discontinue therapy or reduce dose if patient experiences a significant drug related adverse event

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