Therapeutic Class Overview
Electrolyte Depleters

INTRODUCTION

Phosphate Binders

- Hyperphosphatemia, an important and inevitable clinical consequence of advanced stages of chronic kidney disease (CKD), requires appropriate management due to the risk for secondary hyperparathyroidism and cardiovascular disease. Persistent or chronic hyperphosphatemia, along with an elevated calcium times phosphorus (Ca x P) product, is associated with an increased risk of vascular, valvular, and other soft-tissue calcification in patients with CKD. Elevated phosphorus levels may also directly influence several components of CKD-mineral and bone disorder such as secondary hyperparathyroidism, bone abnormalities, calcitriol deficiency, and extraskeletal calcification. In addition, there is evidence consistently demonstrating that hyperphosphatemia is a predictor of mortality in CKD stage 5 patients who are receiving dialysis. Because of these reasons, control of serum phosphorus levels in patients with CKD is an important component of care (*Kidney Disease Improving Global Outcomes [KDIGO] 2009, KDIGO 2017, National Kidney Foundation [NKF] 2003, Kestenbaum et al 2005, Voormolen et al 2007*).
- The 2 principal modalities used to control serum phosphorus levels in patients with CKD include restricting dietary phosphorus intake and administering phosphorus binders (or phosphorus depleters). When dietary phosphorus restriction is inadequate in controlling serum phosphorus levels, the administration of phosphorus binders is recommended. The phosphorus binders class can be divided into 2 subcategories: calcium- and non-calcium-containing products. Calcium-based phosphate binders include calcium carbonate and calcium acetate, and calcium-free binders include aluminum hydroxide, lanthanum carbonate, magnesium carbonate, sevelamer hydrochloride, sevelamer carbonate, ferric citrate, and sucroferric oxyhydroxide. Calcium carbonate's use as a phosphorus binder is off-label and therefore is not detailed in this review.
- The 2017 KDIGO guideline for the diagnosis, evaluation, prevention, and treatment of CKD-mineral and bone disorder (CKD-MBD) does not specifically recommend 1 type of phosphate-binder as first-line therapy, but suggests restricting the dose of calcium-based phosphate binders in adult patients with CKD stage 3a to 5 (with or without dialysis) receiving phosphate-lowering treatment. In children, it is reasonable to base the choice of phosphate-lowering treatment on serum calcium levels *(KDIGO 2017).*
- The sevelamer hydrochloride salt was the initial sevelamer formulation developed; however, because of the incidence of metabolic acidosis associated with its use, a buffered formulation was created. The sevelamer carbonate formulation has advantages compared to sevelamer hydrochloride because it does not lower a patient's bicarbonate level and does not result in the development of metabolic acidosis *(Perry and Plosker 2014)*. An advantage to the use of lanthanum carbonate is a decrease in the pill burden compared to other products (*Prescribing information: Fosrenol 2018, Renagel 2019, Renvela 2018*). Two iron-based, calcium-free phosphate binders are Velphoro (sucroferric oxyhydroxide) and Auryxia (ferric citrate). Velphoro may reduce the pill burden for those patients that require higher doses of sevelamer as demonstrated in trials (*Prescribing information: Auryxia 2019, Velphoro 2020; Wuthrich et al 2013*).
- Available evidence supports the efficacy of all of the phosphorus binders in controlling serum phosphorus levels. It is generally accepted that no one product is effective and acceptable to every patient. Although treatment guidelines recommend serum phosphorus levels to be maintained within or slightly above the normal range (depending on CKD stage), there is currently no evidence to demonstrate that lowering phosphorus to a specific target range results in improved clinical outcomes in patients with CKD. Despite this lack of evidence, it is still reasonable to use phosphorus binders to lower phosphorus levels in CKD patients with hyperphosphatemia to prevent the development of secondary hyperparathyroidism and cardiovascular disease.
- The main considerations for selection of phosphate binders include absorbability, adequate gastrointestinal tolerability, and cost or cost-effectiveness (*Frazão et al 2012*).
- Medispan Therapeutic Class: Phosphate Binder Agents

Table 1. Medications Included Within Class Review - Phosphate Binders

Drug	Generic Availability
Auryxia (ferric citrate)	-
Calphron (calcium acetate)*	✔
Fosrenol (lanthanum carbonate)	✔ †
PhosLo (calcium acetate)	✔
Phoslyra (calcium acetate)	-
Renagel (sevelamer hydrochloride)	✔
Renvela (sevelamer carbonate)	✔
Velphoro (sucroferric oxyhydroxide)	-

*This product is not intended to diagnose, treat, cure or prevent any disease. Calphron is available as an over-the-counter nutritional supplement.
†Fosrenol chewable tablets are available generically; however, the Fosrenol oral powder packet is not generically available.

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020; Calphron 2016*)

Potassium Removing Agents

- Hyperkalemia is a common clinical problem that is most often a result of impaired urinary potassium excretion due to acute or chronic kidney disease and/or disorders or drugs that inhibit the renin-angiotensin-aldosterone system (RAAS). The most serious manifestations of hyperkalemia are muscle weakness or paralysis, cardiac conduction abnormalities, and cardiac arrhythmias, including sinus bradycardia, sinus arrest, slow idioventricular rhythms, ventricular tachycardia, ventricular fibrillation, and asystole. These manifestations usually occur when the serum potassium concentration is ≥ 7 mEq/L with chronic hyperkalemia or possibly at lower levels with an acute rise in serum potassium or in patients with an underlying cardiac conduction disorder (*Mount 2019*).
- There are no clear guidelines regarding the appropriate setting for the treatment of hyperkalemia. The decision for hospital admission for continuous electrocardiograph (ECG) monitoring is a matter of clinical judgment in each case. Patients believed to have a rapid rise in potassium commonly need inpatient care, whereas patients whose hyperkalemia has developed over a period of weeks can often be managed in an outpatient setting with close follow-up (*Hollander-Rodriquez and Calvert 2006, NKF 2016, Rafique et al 2017*).
  - Urgent treatment of hyperkalemia includes 3 main phases: 1) antagonizing cardiac effects of potassium (using intravenous [IV] calcium gluconate); 2) redistributing potassium into cells (using insulin with dextrose, beta-2-adrenergic agonists, or sodium bicarbonate); and 3) removing excess potassium from the body (ie, using hemodialysis, loop diuretics, or cation exchange resins) (*Hollander-Rodriquez and Calvert 2006, Mount 2019, Raebel 2012*).
  - In patients who do not require urgent treatment, lowering total body potassium may be the only step necessary (*Hollander-Rodriquez and Calvert 2006, NKF 2016, Rafique et al 2017*).
- Long-term treatment or prevention of hyperkalemia should be tailored to correcting the underlying cause of hyperkalemia (*Hollander-Rodriquez and Calvert 2006*).
- Cation exchange resins are used in clinical practice for removing excess potassium from the body. Prior to 2015, Kayexalate (sodium polystyrene sulfonate) was the only potassium binding agent approved in the U.S. for the treatment of hyperkalemia; however, the use of sodium polystyrene sulfonate has been limited by tolerability and safety concerns (ie, colonic necrosis and sodium absorption leading to volume overload) and questions about efficacy (*Veltassa FDA Summary Review 2015*).
- In October 2015, the Food and Drug Administration (FDA) approved Veltassa (patiromer), a non-absorbed, cation exchange polymer that contains a calcium-sorbitol counterion, for the treatment of hyperkalemia.
- In May 2018, the FDA approved Lokelma (sodium zirconium cyclosilicate), a non-absorbed zirconium silicate, for the treatment of hyperkalemia in adults.
- Medispan Therapeutic Class: Potassium Removing Agents

Table 2. Medications Included Within Class Review - Potassium Removing Agents

Drug	Generic Availability
Lokelma (sodium zirconium cyclosilicate)	-
sodium polystyrene sulfonate*	✔
Veltassa (patiromer)	-

*Sodium polystyrene sulfonate is generically available; brand Kayexalate is no longer available; Kionex and SPS are branded generics.

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

Table 3. FDA-Approved Indications for Phosphate Binders

Generic name	Reduce absorption of dietary phosphate	Reduce serum phosphate in end stage renal disease	Control serum phosphorus in patients with CKD on dialysis	Iron deficiency anemia in CKD in patients not on dialysis
calcium acetate	✔ (Calphron)	✔ (PhosLo, Phoslyra)		
ferric citrate			✔	✔
lanthanum carbonate		✔		
sevelamer carbonate			✔	
sevelamer hydrochloride			✔*	
sucroferric oxyhydroxide			✔	

*Safety and efficacy in CKD patients who are not on dialysis have not been studied.

(Prescribing information: Auryxia 2019, Calphron 2016, Fosrenol 2020, PhosLo 2013, Phoslyra 2015, Renagel 2020, Renvela 2020, Velphoro 2020)

Table 4. FDA-Approved Indications for Potassium Removing Agents

Generic name	Treatment of hyperkalemia
patiromer	✔
sodium polystyrene sulfonate	✔
sodium zirconium cyclosilicate	✔

(Prescribing information: Lokelma 2020, sodium polystyrene sulfonate powder for suspension 2020, sodium polystyrene sulfonate suspension 2017, Veltassa 2018)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Phosphate Binders

Available evidence supports the efficacy of all of the phosphate binders controlling serum phosphorus levels (*Al-Baaj et al 2005, Almirall et al 2012, Bleyer et al 1999, Block et al 2015, Delmez et al 2007, Dwyer et al 2013, Evenepoel et al 2009, Fan et al 2009, Finn et al 2004, Finn et al 2005, Finn et al 2006, Fischer et al 2006, Fishbane et al 2010, Hervas et al 2003, Hutchison et al 2006, Hutchison et al 2008, Iwasaki et al 2005, Joy et al 2003, Kasai et al 2012, Ketteler et al 2008, Lewis et al 2015, Mehrotra et al 2008, Ouellet et al 2009, Pieper et al 2006, Qunibi et al 2004, Ruospo et al 2018, Shigematsu et al 2008, Shigematsu et al 2010, Sprague et al 2009, St. Peter et al 2008, Suki et al 2007, Wilson et al 2009*).

- In general, the true benefits of phosphorus lowering with respect to hard clinical outcomes have not been established, and most clinical trials evaluated surrogate endpoints. A systematic review of 18 studies evaluated the rate of all-cause mortality among those treated with non-calcium-based phosphate binders compared to calcium-based phosphate binders in patients with CKD (*Jamal et al 2013*). The non-calcium based group which included sevelamer and lanthanum had a statistically significant reduction of 22% in all-cause mortality compared to calcium-based phosphate binders (risk ratio 0.78, 95% confidence interval [CI]: 0.61 to 0.98, I^2 = 43%; 11 randomized clinical trials, N = 4622). Note that 2 observational studies and 1 cross-sectional study were included. No significant reduction in cardiovascular events was observed.
- Clinical trials have consistently demonstrated that sevelamer hydrochloride is effective at lowering phosphorus levels and maintaining phosphate control comparable to calcium acetate and calcium carbonate therapy (*Bleyer et al 1999, Evenepoel et al 2009, Hervas et al 2003, Pieper et al 2006, Qunibi et al 2004).* A 2018 systematic review concluded that sevelamer may lower death from all causes and significantly decrease the risk of hypercalcemia compared with calcium-based agents (*Ruospo et al 2018*). A 2016 meta-analysis of 25 studies with 88% of patients on hemodialysis found lower all-cause mortality with sevelamer (risk ratio 0.54, 95% CI: 0.32 to 0.93) compared to calcium-based binders, but no statistical difference for cardiovascular mortality was observed (*Patel et al 2016*).
- Clinical trials demonstrate that lanthanum carbonate and sevelamer show comparable efficacy in lowering phosphorous although limited studies have compared the 2 therapies for efficacy (*Kasai et al 2012*). Findings from a meta-analysis showed that, compared with calcium-based agents, lanthanum significantly decreased the risk for hypercalcemia but had similar effects on phosphate levels (*Ruospo et al 2018*). A randomized controlled trial also found similar effects on phosphorus levels with lanthanum compared to calcium acetate at the 1-year mark (*Kovesdy et al 2018*).
- The efficacy and safety of sucroferric oxyhydroxide were evaluated in 3 trials: a fixed dose study, a dose titration study, and a dose titration extension study. Sucroferric oxyhydroxide demonstrated efficacy by significantly reducing serum phosphorus in hemodialysis and peritoneal dialysis patients from 6 to 52 weeks (*Velphoro prescribing information 2020, Wuthrich et al 2013*).
  - In the fixed dose study, all sucroferric oxyhydroxide dose groups showed a significant decrease in serum phosphorus ($p \leq 0.02$), except the 250 mg/day group. The proportion of sucroferric oxyhydroxide-treated patients achieving goal phosphorus levels after 6 weeks of treatment ranged from 35 to 60% for 1000 to 2500 mg/day, and 42.1% in the sevelamer control arm. The median time to reach first controlled serum phosphorus levels was not different for sucroferric oxyhydroxide (1 week) vs the sevelamer (2 weeks) control arm ($p > 0.16$) (*Wuthrich et al 2013*).
  - In the dose titration study, sucroferric oxyhydroxide 1000 to 3000 mg/day was statistically superior to the sucroferric oxyhydroxide low dose (250 mg) control in maintaining the phosphorus-lowering effect in hemodialysis patients at week 27 ($p < 0.001$) (*Floege et al 2014*). In the extension trial, sucroferric oxyhydroxide demonstrated a greater change from baseline in serum phosphorus when compared to sevelamer carbonate from weeks 32 to 40. However, from weeks 44 to 52, changes in serum phosphorus between sevelamer carbonate and sucroferric oxyhydroxide were similar (*Floege et al 2015*). The greatest changes from baseline for serum phosphorus occurred up to week 12 for sevelamer carbonate and up to week 20 for sucroferric oxyhydroxide (*Velphoro prescribing information 2020*).
  - The most frequent adverse events were hypophosphatemia and discolored feces for the sucroferric oxyhydroxide groups. Sucroferric oxyhydroxide patients experienced more discolored feces, hypophosphatemia, muscle spasms, and constipation compared to sevelamer HCl in the active comparator trial (*Wuthrich et al 2013*).
- Ferric citrate is an iron-based, calcium-free phosphate binder that has been studied in several published trials. Ferric citrate is similarly safe and effective to 2 current first-line phosphate binders, calcium acetate and sevelamer (*Lewis et al 2015*). Ferric citrate offers a reduced pill burden vs sevelamer carbonate but not vs calcium acetate. In addition to reducing serum phosphorus, ferric citrate raises iron stores (evidenced by increased hemoglobin, serum ferritin, and serum transferrin saturation) and decreases IV iron and erythropoietin stimulating agent usage (*Auryxia Prescribing Information 2019, Block et al 2015, Lewis et al 2015, Umanath et al 2015*).

Potassium Removing Agents

- The FDA first approved sodium polystyrene sulfonate in 1958, 4 years before passage of the Kefauver-Harris Drug Amendment, which requires drug manufacturers to prove the effectiveness of their products before marketing (*Sterns et al 2010*).
  - In 1961, Scherr et al reported the largest clinical experience with sodium polystyrene sulfonate suspended in water in an uncontrolled study of hyperkalemic patients with acute and chronic renal failure, using the newly approved sodium polystyrene sulfonate. In 23 of 30 cases, the plasma potassium fell by at least 0.4 mEq/L in the first 24 hours. Two

patients with pre-treatment potassium levels of 6.1 and 7.4 mEq/L developed hypokalemia (3.3 and 2.3 mEq/L) while receiving 40 g/day of oral resin for 2 and 6 days. On the strength of this study and several smaller case series, the FDA's Drug Efficacy Study Implementation (DESI) Program, charged with reviewing pre-1962 drugs that were already on the market, ruled sodium polystyrene sulfonate powder "effective" (*Sterns et al 2010*).

- A randomized, double-blind, placebo-controlled, single-center study (n = 33) evaluated the safety and efficacy of a 7-day course of sodium polystyrene sulfonate in the treatment of mild hyperkalemia (potassium levels of 5.0 to 5.9 mEq/L) in patients with CKD (*Lepage et al 2015*).
  - Sodium polystyrene sulfonate was superior to placebo in the reduction of serum potassium levels (mean difference between groups: −1.04 mEq/L; 95% CI: −1.37 to −0.71). A higher proportion of patients in the sodium polystyrene sulfonate group attained normokalemia at the end of their treatment compared with those in the placebo group, but the difference did not reach statistical significance (73% vs 38%, p = 0.07).
- The safety and efficacy of patiromer were based primarily on 2 pivotal trials in hyperkalemic patients (potassium levels of 5.1 to < 6.5 mEq/L).
  - OPAL-HK was a 2-part, single-blind, Phase 3 study that evaluated the efficacy and safety of patiromer in 237 patients with CKD receiving RAAS inhibitors. During the initial treatment phase (Part A), patiromer therapy resulted in a mean (± standard error [SE]) change from baseline to week 4 in serum potassium of −1.01 ± 0.03 mEq/L (95% CI: −1.07 to −0.95; p < 0.001) (*Weir et al 2015*).
    - Patients with moderate to severe hyperkalemia at baseline who achieved a target potassium level with initial treatment during Part A were randomized to receive patiromer (n = 55) or placebo (n = 52) in Part B (randomized withdrawal phase). The median increase in potassium level from baseline of Part B through week 4 was greater with placebo compared with patiromer (0.72 mEq/L vs 0 mEq/L, 95% CI: 0.46 to 0.99; p < 0.001).
  - AMETHYST-DN was a long-term, Phase 2, randomized study in patients with CKD and diabetes mellitus receiving a RAAS inhibitor. Patiromer demonstrated a mean change from baseline to week 4 or at first patiromer dose titration in serum potassium of −0.35 mEq/L (95% CI: −0.22 to −0.48, p < 0.001) in patients with mild hyperkalemia receiving 8.4 g/day and −0.87 mEq/L (95% CI: −0.60 to −1.14, p < 0.001) in patients with moderate hyperkalemia receiving 16.8 g/day. The efficacy of patiromer was maintained for 1 year (*Bakris et al 2015*).
- The safety and efficacy of sodium zirconium cyclosilicate were based on data from 2 double-blind, placebo-controlled studies and 2 open-label studies in adult patients with hyperkalemia.
  - Study 1 was a 2-part, Phase 3, double-blind, randomized controlled trial in patients with hyperkalemia (> 5 mmol/L). Patients were randomly assigned to receive either sodium zirconium cyclosilicate (at a dose of 1.25 g, 2.5 g, 5 g, or 10 g) or placebo 3 times daily for 48 hours. Patients with normokalemia (serum potassium level, 3.5 to 4.9 mmol/L) at 48 hours were randomly assigned to receive either sodium zirconium cyclosilicate or placebo once daily on days 3 to 14 (maintenance phase). The primary endpoint was the exponential rate of change in the mean serum potassium level at 48 hours *(Packham et al 2015)*.
    - At 48 hours, the mean serum potassium level had decreased from 5.3 mmol/L at baseline to 4.9 mmol/L in the group of patients who received 2.5 g of sodium zirconium cyclosilicate, 4.8 mmol/L in the 5 g group, and 4.6 mmol/L in the 10 g group, for mean reductions of 0.5, 0.5, and 0.7 mmol/L, respectively (p < 0.001 for all comparisons) and to 5.1 mmol/L in the 1.25 g group and the placebo group (mean reduction, 0.3 mmol/L). In patients who received 5 g of sodium zirconium cyclosilicate and those who received 10 g of sodium zirconium cyclosilicate, serum potassium levels were maintained at 4.7 mmol/L and 4.5 mmol/L, respectively, during the maintenance phase, as compared with a level of more than 5.0 mmol/L in the placebo group (p < 0.01 for all comparisons).
  - Study 2 (HARMONIZE) was a Phase 3, randomized, double-blind, placebo-controlled trial evaluating sodium zirconium cyclosilicate in outpatients with hyperkalemia (serum potassium ≥ 5.1 mEq/L). Patients (n = 258) received 10 g of sodium zirconium cyclosilicate 3 times daily in the initial 48-hour open-label phase. Patients (n = 237) achieving normokalemia (3.5 to 5.0 mEq/L) were then randomized to receive sodium zirconium cyclosilicate, 5 g (n = 45 patients), 10 g (n = 51), or 15 g (n = 56), or placebo (n = 85) daily for 28 days *(Kosiborod et al 2014)*.
    - In the open-label phase, serum potassium levels declined from 5.6 mEq/L at baseline to 4.5 mEq/L at 48 hours, with 84% of patients (95% CI: 79 to 88) achieving normokalemia by 24 hours and 98% (95% CI: 96 to 99) by 48 hours. In the randomized phase, serum potassium was significantly lower during days 8 to 29 with all 3 sodium zirconium cyclosilicate doses vs placebo (4.8 mEq/L [95% CI: 4.6 to 4.9], 4.5 mEq/L [95% CI: 4.4 to 4.6], and 4.4 mEq/L [95% CI: 4.3 to 4.5] for 5 g, 10 g, and 15 g; 5.1 mEq/L [95% CI: 5.0 to 5.2] for placebo; p < 0.001 for all comparisons).

- Patients who completed the 28-day randomized withdrawal phase had the option to continue treatment with sodium zirconium cyclosilicate, in an open-label extension phase for up to 11 months (n = 123). The treatment effect on serum potassium was maintained during continued therapy *(Lokelma Prescribing Information, Roger et al 2019)*.
- The same study protocol was performed in Japan, Russia, South Korea, and Taiwan (HARMONIZE-Global). Maintenance of normokalemia was higher in the 5 g group (58.6%) and 10 g group (77.3%) compared to placebo (24%) (p<0.001 for all comparisons) (*Zannad et al 2020).*

- Sodium zirconium cyclosilicate was also evaluated in an open-label 12-month study in 751 hyperkalemic patients. The mean baseline potassium level in this study was 5.6 mEq/L. Following the acute phase treatment of sodium zirconium cyclosilicate 10 g 3 times a day, patients who achieved normokalemia (3.5 to 5.0 mEq/L) within 72 hours (n = 746; 99%) entered the maintenance phase. For maintenance treatment, the initial dosage was 5 g once daily and was adjusted to a minimum of 5 g every other day up to maximum of 15 g once daily, based on serum potassium level. The treatment effect on serum potassium was maintained during continued therapy, regardless of whether glomerular filtration rate was < 30 or ≥ 30 mL/min/1.73m^2 *(Lokelma Prescribing Information 2020, Spinowitz et al 2019, Roger et al 2020)*.
- The safety and efficacy of sodium zirconium cyclosilicate were evaluated in patients with end stage renal disease (ESRD) receiving hemodialysis through a double-blind, placebo-controlled, Phase 3b randomized clinical trial. A total of 196 patients with pre-dialysis hyperkalemia were randomized to receive either placebo or sodium zirconium cyclosilicate 5 g daily on non-dialysis days, with the option of titrating to 15 g daily. A total of 41.2% of patients receiving sodium zirconium cyclosilicate achieved a pre-dialysis potassium serum level between 4.0 and 5.0 mmol/L following 4 weeks of therapy compared to 1.0% in the placebo group (p<0.001) *(Fishbane et al 2019)*.

CLINICAL GUIDELINES

KDIGO - Clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of CKD-MBD *(KDIGO 2009, KDIGO 2017)*

- KDIGO published treatment guidelines in 2009 and these were updated again in 2017. The update revised recommendations for treatment of elevated phosphate levels. The recommendations include:
  - In patients with CKD stage 3a to 5 (with or without dialysis), KDIGO suggests lowering elevated phosphate levels toward the normal range. There is insufficient evidence that maintaining phosphate in the normal range is of clinical benefit to CKD stage 3a to stage 4 patients. Due to safety concerns with pharmacologic therapy, treatment should be reserved for overt hyperphosphatemia.
  - In patients with CKD stage 3 to stage 5 (with or without dialysis), decisions about phosphate-lowering treatment should be based on progressively or persistently elevated serum phosphate. The broader term “phosphate-lowering” treatment is used instead of phosphate binding agents since all possible approaches (ie, binders, diet, or dialysis) can be effective.
  - In adult patients with CKD stage 3a to 5 (with or without dialysis) receiving phosphate-lowering treatment, KDIGO suggests restricting the dose of calcium-based phosphate binder. In children, it is reasonable to base the choice of phosphate-lowering treatment on serum calcium levels.

- **KDOQI – US Commentary on the 2017 KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of CKD-MBD** *(Isakova 2017)*
  - The KDOQI CKD-MBD work group published a commentary on the 2017 KDIGO guideline update recommendations.
  - The majority of the KDOQI work group supported the recommendation from the 2017 KDIGO guideline to limit calcium-based binders *when possible*, and discussed that there are multiple non-calcium phosphate-lowering therapies that are effective with similar adverse event profiles to calcium-based phosphate binders. The work group endorsed the recommendation to base the choice of phosphate-lowering therapy in children on serum calcium levels.

SAFETY SUMMARY

Phosphate Binders

- Sevelamer carbonate and sevelamer hydrochloride are contraindicated in patients with bowel obstruction. Cases of dysphagia, bowel obstruction and perforation, and esophageal tablet retention have been reported in association with use of the tablet formulation of sevelamer, some requiring hospitalization and intervention. Inflammatory disorders may resolve upon sevelamer discontinuation. The sevelamer suspension formulation should be considered in patients with a history of swallowing disorders. Adverse effects possibly related to sevelamer included nausea, vomiting, dyspepsia,

diarrhea, flatulence, abdominal pain, and constipation. Ciprofloxacin should be taken at least 2 hours before or 6 hours after sevelamer, and mycophenolate mofetil should be taken at least 2 hours before sevelamer.

- Calcium acetate is contraindicated in patients with hypercalcemia. Calcium supplements should be used with caution in patients with CKD due to the increased risk of developing hypercalcemia. The most common adverse effects include hypercalcemia, nausea, and vomiting. Diarrhea has been reported with calcium acetate oral solution. The administration of calcium acetate may decrease the bioavailability of tetracyclines or fluoroquinolones.
- Ferric citrate is contraindicated in patients with iron overload. Ferric citrate should be kept out of the reach of children to lower the risk of accidental overdose of iron. Adverse events reported in > 5% of patients treated with ferric citrate in clinical trials included diarrhea, nausea, constipation, vomiting, discolored feces, abdominal pain, hyperkalemia, and cough. Doxycycline should be taken at least 1 hour before ferric citrate. Ciprofloxacin should be taken at least 2 hours before or after ferric citrate.
- Bowel obstruction, ileus, and fecal impaction are contraindications to lanthanum carbonate therapy. Serious adverse events consisting of gastrointestinal obstruction, ileus, subileus, gastrointestinal perforation, and/or fecal impaction have been reported with this medication, and some of these events required surgery or hospitalization. Adverse events that were more commonly associated with lanthanum carbonate therapy included nausea, vomiting, and abdominal pain. Compounds that bind aluminum-, magnesium-, or calcium-based cationic antacids and thyroid hormone replacement therapy should be separated by at least 2 hours from lanthanum carbonate. Fluoroquinolones should be taken at least 1 hour before or 4 hours after lanthanum. Patients should be advised to chew lanthanum carbonate tablets completely and to not swallow them whole. Serious gastrointestinal complications have been associated with unchewed or incompletely chewed tablets.
- Sucroferric oxyhydroxide does not have any contraindications. Due to the potential for drug interactions, levothyroxine should be taken at least 4 hours before sucroferric oxyhydroxide. Doxycycline, acetylsalicylic acid, and cephalexin must be taken at least 1 hour before sucroferric oxyhydroxide. Common adverse events include dark/discolored feces, nausea, and diarrhea.

Potassium Removing Agents

- Patiromer is contraindicated in patients with known hypersensitivity to patiromer or any of its components. Warnings and precautions of patiromer include worsening of gastrointestinal motility and hypomagnesemia. The most common adverse effects (≥ 2%) with patiromer use were constipation, hypomagnesemia, diarrhea, nausea, abdominal discomfort, and flatulence.
- Sodium polystyrene sulfonate powder for suspension is contraindicated in patients with obstructive bowel disease and neonates with reduced gut motility. Sodium polystyrene sulfonate suspension is contraindicated in patients with hypokalemia, obstructive bowel disease, as oral administration in neonates, and in neonates with reduced gut motility. Warnings and precautions for sodium polystyrene sulfonate include intestinal necrosis; development of hypokalemia or other electrolyte disturbances; fluid overload in patients sensitive to high sodium intake; and risk of aspiration.
  - Sodium polystyrene sulfonate may cause some degree of gastric irritation. Anorexia, nausea, vomiting, and constipation may occur especially if high doses are given. Occasionally diarrhea develops.
- Sodium zirconium cyclosilicate does not have any contraindications. Warnings and precautions for sodium zirconium cyclosilicate include gastrointestinal adverse events in patients with motility disorders, edema, and hypokalemia in hemodialysis patients. The most common adverse effect was mild to moderate edema.

DOSING AND ADMINISTRATION

Table 5. Dosing and Administration of Phosphate Binders

Generic name	Available Formulations	Route	Usual Recommended Frequency	Comments
calcium acetate	Capsule, tablet, solution	Oral	Administered with each meal	--
ferric citrate	Tablet	Oral	Three times daily with meals	--

Generic name	Available Formulations	Route	Usual Recommended Frequency	Comments
lanthanum carbonate	Chewable tablet, powder	Oral	Administered with meals or immediately after meals	• Use is not recommended in children. In animal studies, lanthanum was deposited into developing bone including the growth plate. Consequences of lanthanum bone deposition are unknown.
sevelamer carbonate	Powder for oral suspension, tablet	Oral	Three times daily with meals	--
sevelamer hydrochloride	Tablet	Oral	Three times daily with meals	--
sucroferric oxyhydroxide	Chewable tablet	Oral	Three times daily with meals	--

See the current prescribing information for full details

Table 6. Dosing and Administration of Potassium Removing Agents

Generic name	Available Formulations	Route	Usual Recommended Frequency	Comments
patiromer	Powder for suspension	Oral	Once daily with or without food	• Administer at least 3 hours before or 3 hours after other oral medications. • Do not administer in its dry form.
sodium polystyrene sulfonate	Powder for suspension; suspension	Oral; rectal (enema)	Oral: 1 to 4 times daily Rectal: Every 6 hours	• Administer at least 3 hours before or 3 hours after other oral medications. • Patients with gastroparesis may require a 6-hour separation.
sodium zirconium cyclosilicate	Powder for suspension	Oral	Starting dose is 10 g administered 3 times daily for up to 48 hours; for maintenance, recommended dose is 10 g once daily or 5 g once daily on non-dialysis days for hemodialysis patients	• Other oral medications should be administered at least 2 hours before or 2 hours after sodium zirconium cyclosilicate.

CONCLUSION

Phosphate Binders

- The phosphorus binders (or phosphorus depleters) class is an important aspect of the medical management of patients with CKD; these agents are used to lower a patient's phosphorus level. If phosphorus levels remain elevated in this population, the patient is at a greater risk for the development of secondary hyperparathyroidism or cardiovascular disease. In addition, there is available evidence to demonstrate that hyperphosphatemia is a predictor of mortality in CKD stage 5 patients who are receiving dialysis. In patients with CKD stage 3 to stage 5 (with or without dialysis), decisions about phosphate-lowering treatment should be based on progressively or persistently elevated serum phosphate. The broader term "phosphate-lowering" treatment is used instead of phosphate binding agents since all possible approaches (ie, binders, diet, or dialysis) can be effective (*NKF 2003, KDIGO 2009, KDIGO 2017*).
- The 2 subgroups of phosphorus binders currently available include the calcium and non-calcium containing products. Available evidence supports the efficacy of all of the phosphorus binders in controlling serum phosphorus levels. It is important to note that although the true benefits of these agents, with respect to hard clinical outcomes, have not been established, it is still reasonable to prescribe these products in patients with CKD who have elevated phosphorus levels to prevent the development of secondary hyperparathyroidism and cardiovascular disease.

- In adult patients with CKD stage 3a to 5 (with or without dialysis) receiving phosphate-lowering treatment, KDIGO suggests restricting the dose of calcium-based phosphate binder. In children, it is reasonable to base the choice of phosphate-lowering treatment on serum calcium levels *(KDIGO 2017).*
- Sevelamer, a non-calcium-containing phosphate binder, is available in 2 salt formulations: hydrochloride (Renagel) and carbonate (Renvela). The hydrochloride formulation was developed first, but due to the incidence of metabolic acidosis associated with its use, a buffered sevelamer formulation was later developed. The sevelamer carbonate product will most likely be preferred in this patient population due to a decrease in the incidence of metabolic acidosis associated with its use. Additionally, sevelamer carbonate is the only phosphate binder that is FDA-approved for use in children (6 years of age and older).
- Lanthanum carbonate (Fosrenol) is another non-calcium-containing phosphorus binder available. An advantage to this agent, in addition to not causing an increase in serum calcium levels, appears to be its decreased pill burden compared to the other products (*NKF 2003, KDIGO 2009*).
- Two iron-based, calcium-free phosphate binders are now available.
  - Sucroferric oxyhydroxide provides long-term control of hyperphosphatemia, as demonstrated by the 52-week extension trial (*Floege et al 2015*). Sucroferric oxyhydroxide may reduce the pill burden for those patients that require higher doses of sevelamer as demonstrated in trials (*Wuthrich et al 2013*).
  - Ferric citrate has shown to provide significant reductions in serum phosphate levels in 3 studies (*Block et al 2015, Dwyer et al 2013, Lewis et al 2015*). Based on secondary study endpoints, ferric citrate raises iron stores (evidenced by increased serum ferritin and serum transferrin saturation) and decreases IV iron and erythropoietin stimulating agent usage (*Lewis et al 2015, Umanath et al 2015*). Ferric citrate's effects may make it an attractive option for dialysis patients who require concomitant use of a phosphate binder and anemia treatments.
- The main considerations for selection of phosphate binders include absorbability, adequate gastrointestinal tolerability, and cost or cost-effectiveness (*Frazão et al 2012*).

Potassium Removing Agents

- Hyperkalemia is a common clinical problem that is most often a result of impaired urinary potassium excretion due to acute or chronic kidney disease and/or disorders or drugs that inhibit the RAAS may also cause hyperkalemia *(Mount 2019)*.
- Acute or urgent treatment of hyperkalemia includes 3 main phases: 1) antagonizing cardiac effects of potassium by using IV calcium gluconate; 2) redistributing potassium into cells using insulin with dextrose, beta-2-adrenergic agonists, or sodium bicarbonate; and 3) removing excess potassium from the body using hemodialysis, loop diuretics, or cation exchange resins (ie, sodium polystyrene sulfonate) (*Hollander-Rodriquez et al 2006, Mount 2019, Raebel 2012*).
  - In patients who do not require urgent treatment, lowering total body potassium may be the only step necessary (*Hollander-Rodriquez et al 2006*).
- In October 2015, the FDA approved Veltassa (patiromer), a non-absorbed, cation exchange polymer that contains a calcium-sorbitol counterion, for the treatment of hyperkalemia. Patiromer should not be used as an emergency treatment for life-threatening hyperkalemia because of its delayed onset of action.
- Patiromer has been shown to be effective in lowering serum potassium levels in patients with CKD receiving RAAS inhibitor therapy. Patiromer has also been shown to provide sustained reductions of serum potassium for up to 1 year.
  - Compared with sodium polystyrene sulfonate, patiromer has more robust prospective long-term data and may have a more favorable adverse event profile (sodium polystyrene sulfonate is associated with intestinal necrosis and sodium retention). Studies used for the approval of patiromer did not address the relative efficacy and safety of patiromer vs sodium polystyrene sulfonate.
  - In addition, the role of patiromer for the outpatient treatment of hyperkalemia is unknown, as chronic management of hyperkalemia is generally accomplished through dietary modifications, discontinuation or dose lowering of hyperkalemia-exacerbating agents, or the use of diuretics.
- In May 2018, the FDA also approved Lokelma (sodium zirconium cyclosilicate), a non-absorbed zirconium silicate that acts as a highly-selective potassium-removing agent, for the treatment of hyperkalemia. Similar to patiromer, sodium zirconium cyclosilicate should not be used as an emergency treatment for life-threatening hyperkalemia because of its delayed onset of action. The safety and efficacy of sodium zirconium cyclosilicate were based on data from 2 double-blind, placebo-controlled studies and 2 open-label studies in adult patients with hyperkalemia.

- The placebo-controlled studies demonstrated that patients treated with sodium zirconium cyclosilicate had significant reductions in serum potassium levels vs placebo-treated patients. The 2 open-label studies showed that the treatment effect of sodium zirconium cyclosilicate on serum potassium was maintained during continued therapy.

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