

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 (CKD-MBD) 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 phosphate binders. When dietary phosphorus restriction is inadequate in controlling serum phosphorus levels, the administration of phosphate binders is recommended. The phosphate binder class can be divided into 2 subcategories: calcium- and non-calcium-containing products. Calcium-based phosphate binders include calcium carbonate and calcium acetate; calcium-free binders include aluminum hydroxide, lanthanum carbonate, magnesium carbonate, sevelamer hydrochloride, sevelamer carbonate, ferric citrate, and sucroferric oxyhydroxide. The use of calcium carbonate (available over-the-counter) 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-MBD does not specifically recommend one 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 2020, Renagel 2020, Renvela 2020*). Two iron-based, calcium-free phosphate binders are Velphoro (sucroferric oxyhydroxide) and Auryxia (ferric citrate). Velphoro may reduce the pill burden for those patients who require higher doses of sevelamer as demonstrated in trials (*Prescribing information: Auryxia 2021, 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 (GI) 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)	-
Fosrenol (lanthanum carbonate)	✓ *
PhosLo (calcium acetate) [†]	✓
Phoslyra (calcium acetate)	-
Renagel (sevelamer hydrochloride)	✓
Renvela (sevelamer carbonate)	✓
Velphoro (sucroferric oxyhydroxide)	-

* Fosrenol chewable tablets are available generically; however, the Fosrenol oral powder packet is not generically available.

[†] Calcium acetate 667 mg tablets are also available over-the-counter (Calphron).

(*Drugs@FDA 2021, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021*)

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 2020*).
- There are no clear guidelines regarding the appropriate setting for the treatment of hyperkalemia. The decision for hospital admission for continuous electrocardiogram (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-Rodriguez 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-Rodriguez and Calvert 2006, Mount 2020, Raebel 2012*).
 - In patients who do not require urgent treatment, lowering total body potassium may be the only step necessary (*Hollander-Rodriguez 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-Rodriguez 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 United States 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 Food and Drug Administration [FDA] Summary Review 2015*).
- 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.
- 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; SPS is a branded generic.

(*Drugs@FDA 2021, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021*)

INDICATIONS

Table 3. FDA-Approved Indications for Phosphate Binders

Generic name	Reduce serum phosphate in end stage renal disease	Adjunct to reduction in dietary intake of phosphate and dialysis to reduce serum phosphorus in patients with kidney failure on dialysis	Control serum phosphorus in patients with CKD on dialysis	Iron deficiency anemia in CKD in patients not on dialysis
calcium acetate	✓ (PhosLo)	✓ (Phoslyra)		
ferric citrate			✓	✓
lanthanum carbonate	✓			
sevelamer carbonate			✓*	
sevelamer hydrochloride			✓†	
sucroferric oxyhydroxide			✓	

* in adults and children 6 years of age and older †Safety and efficacy in CKD patients who are not on dialysis have not been studied.

(*Prescribing information: Auryxia 2021, Fosrenol 2020, PhosLo 2013, Phoslyra 2020, 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	✓

*Should not be used as an emergency treatment for life-threatening hyperkalemia

(*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.

SUMMARY

Phosphate Binders

Available evidence supports the efficacy of all of the phosphate binders for 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 have 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 phosphorus 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 2021, Block et al 2015, Lewis et al 2015, Umanath et al 2015, Choi 2020*).

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 patiomer 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 patiomer in 237 patients with CKD receiving RAAS inhibitors. During the initial treatment phase (Part A), patiomer therapy resulted in a mean (\pm 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 patiomer (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 patiomer (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. Patiomer demonstrated a mean change from baseline to week 4 or at first patiomer 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 patiomer 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 \geq 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 2020, 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/1.73m² (*Lokelma Prescribing Information 2020, Spinowitz et al 2019, Roger et al 2021*).
- 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*).
- A 2020 Cochrane review of 15 randomized controlled trials (RCTs) evaluated the evidence on the effectiveness and tolerability of potassium binders in patients with CKD and chronic hyperkalemia ($n = 1849$). Twelve of the 15 studies included patients with CKD not on dialysis and 3 studies were in patients receiving dialysis. Calcium polystyrene sulfonate, sodium polystyrene sulfonate, patiromer, and sodium zirconium cyclosilicate were the potassium binders studied in the included trials. Ten studies compared a potassium binder to placebo. Little to no effect on mortality was observed with patiromer or sodium zirconium cyclosilicate vs placebo. Impact on mortality was not evaluated with the older agents, calcium or sodium polystyrene sulfonate. There was no apparent impact of these agents on GI-related symptoms (nausea, diarrhea, constipation, vomiting) or quality of life. No studies evaluated the impact on cardiac arrhythmias or major GI events. The authors concluded that the current evidence comparing different potassium binders vs placebo on outcomes of cardiac arrhythmias or major GI events is lacking (*Natale et al 2020*).

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.
- **Kidney Disease Outcomes Quality Initiative (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.
- **NKF - Best practices in managing hyperkalemia in CKD (NKF 2016)**
 - Although not a guideline, NKF's best practices provides a general guide to clinicians on management of acute and chronic hyperkalemia in patients with CKD.
 - Chronic hyperkalemia requires ongoing pharmacologic and non-pharmacologic interventions.
 - In addition to monitoring dietary potassium, pharmacologic options include fludrocortisone acetate for patients with aldosterone deficiency, cation exchange resins such as sodium polystyrene sulfonate, and patiromer. Sodium zirconium cyclosilicate is not listed as this agent became available after the best practices document was published.

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 and may be more pronounced when administered with nutritional supplements containing maltitol. The administration of calcium acetate may decrease the bioavailability of tetracyclines, fluoroquinolones or levothyroxine (Phoslyra).
- 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 GI obstruction, ileus, subileus, GI 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 GI 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 GI motility and hypomagnesemia. The most common adverse effects ($\geq 2\%$) 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 GI 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	● Do not crush or chew because it may cause discoloration of teeth and mouth.
lanthanum carbonate	Chewable tablet, powder	Oral	Administered with meals or immediately after meals	<ul style="list-style-type: none"> ● 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. ● Powder can be considered in patients with poor dentition or difficulty swallowing tablets.
sevelamer carbonate	Powder for oral suspension, tablet	Oral	Three times daily with meals	<ul style="list-style-type: none"> ● Dose in adults is based on serum phosphorus levels. ● Dose in pediatric patients should be based on body surface area.
sevelamer hydrochloride	Tablet	Oral	Three times daily with meals	--
sucroferric oxyhydroxide	Chewable tablet	Oral	Three times daily with meals	● Tablets should be chewed or crushed and not swallowed whole.

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	<ul style="list-style-type: none"> ● 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	<ul style="list-style-type: none"> ● Administer at least 3 hours before or 3 hours after other oral medications. ● Patients with gastroparesis may require a 6-hour separation. ● The enema should be retained as long as possible and followed by a cleansing enema.
sodium zirconium cyclosilicate	Powder for suspension	Oral	Starting dose is 10 g administered 3 times daily for up to 48	● Other oral medications should be administered at least 2 hours before or 2

Generic name	Available Formulations	Route	Usual Recommended Frequency	Comments
			hours; for maintenance, recommended dose is 10 g once daily or 5 g once daily on non-dialysis days for hemodialysis patients	hours after sodium zirconium cyclosilicate.

CONCLUSION

Phosphate Binders

- The phosphate binders (or phosphate 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 phosphate binders currently available include the calcium and non-calcium containing products. Available evidence supports the efficacy of all of the phosphate 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 phosphate binder. 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 been 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 GI 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 (*Mount 2020*).

- 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-Rodriguez et al 2006, Mount 2020, Raebel 2012).
 - In patients who do not require urgent treatment, lowering total body potassium may be the only step necessary (Hollander-Rodriguez et al 2006).
- In October 2015, the FDA approved Veltassa (patiomer), a non-absorbed, cation exchange polymer that contains a calcium-sorbitol counterion, for the treatment of hyperkalemia. Patiomer should not be used as an emergency treatment for life-threatening hyperkalemia because of its delayed onset of action.
- In a randomized withdrawal study, patiomer has been shown to be effective in lowering serum potassium levels in patients with CKD receiving RAAS inhibitor therapy. Patiomer has also been shown to provide sustained reductions of serum potassium for up to 1 year.
 - Compared with sodium polystyrene sulfonate, patiomer 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), although the pivotal trials for patiomer did not address its relative efficacy and safety vs sodium polystyrene sulfonate.
 - In addition, the role of patiomer 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 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 patiomer, 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.

REFERENCES

- Al-Baaj F, Speake M, Hutchison AJ. Control of serum phosphate by oral lanthanum carbonate in patients undergoing hemodialysis and continuous ambulatory peritoneal dialysis in a short-term, placebo-controlled study. *Nephrol Dial Transplant*. 2005;20(4):775-782.
- Almirall J, Betancourt L, Esteve V, et al. Clinical usefulness of lanthanum carbonate for serum phosphate control in difficult patients. *Int Urol Nephrol*. 2012 Feb;44(1):231-236.
- Auryxia [package insert]. Boston, MA: Keryx Biopharmaceuticals, Inc.; March 2021.
- Bakris GL, Pitt B, Weir MR, et al. Effect of patiomer on serum potassium levels in patients with hyperkalemia and diabetic kidney disease: The AMETHYST-DN randomized clinical trial. *JAMA*. 2015;314(2):151-161.
- 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.
- Block GA, Fishbane S, Rodriguez M, et al. A 12-week, double-blind, placebo-controlled trial of ferric citrate for the treatment of iron deficiency anemia and reduction of serum phosphate in patients with CKD stages 3-5. *Am J Kidney Dis*. 2015;65(5):728-736.
- Choi YJ, Noh Y, Shin S. Ferric citrate in the management of hyperphosphatemia and iron deficiency anaemia: a meta-analysis in patients with chronic kidney disease. *Br J Clin Pharmacol*. 2020. doi: 10.1111/bcp.14396.
- Delmez J, Block G, Robertson J, et al. A randomized, double-blind, crossover design study of sevelamer hydrochloride and sevelamer carbonate in patients on hemodialysis. *Clin Nephrol*. 2007;68(6):386-391.
- Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2021. <http://www.accessdata.fda.gov/scripts/cder/daf/>. Accessed May 1, 2021.
- Dwyer JP, Sika M, Schulman G, et al. Dose-response and efficacy of ferric citrate to treat hyperphosphatemia in hemodialysis patients: a short-term randomized trial. *Am J Kidney Dis*. 2013;61(5):759-766.
- Evenepoel P, Selgas R, Caputo F, et al. Efficacy and safety of sevelamer hydrochloride and calcium acetate in patients on peritoneal dialysis. *Nephrol Dial Transplant*. 2009;24(1):278-285.
- Fan S, Ross C, Mitra S, et al. A randomized, crossover design study of sevelamer carbonate powder and sevelamer hydrochloride tablets in chronic kidney disease in patients on hemodialysis. *Nephrol Dial Transplant*. 2009;24(12):3794-3799.
- Finn WF, Joy MS, Hladik G, Lanthanum Study Group. Efficacy and safety of lanthanum carbonate for reduction of serum phosphorus in patients with chronic renal failure receiving hemodialysis. *Clin Nephrol*. 2004;62(3):193-201.
- Finn WF, Joy MS. A long-term, open-label extension study on the safety of treatment with lanthanum carbonate, a new phosphate binder, in patients receiving hemodialysis. *Curr Med Res Opin*. 2005;21(5):657-664.
- Finn WF, SPD 405-307 Lanthanum Study Group. Lanthanum carbonate vs standard therapy for the treatment of hyperphosphatemia: safety and efficacy in chronic maintenance hemodialysis patients. *Clin Nephrol*. 2006;65(3):191-202.

- Fischer D, Cline K, Plone MA, et al. Results of a randomized crossover study comparing once-daily and thrice-daily sevelamer dosing. *Am J Kidney Dis.* 2006;48(3):437-444.
- Fishbane S, Delmez J, Suki WN, et al. A randomized, parallel, open-label study to compare once-daily sevelamer carbonate powder dosing with thrice-daily sevelamer hydrochloride tablet dosing in CKD patients on hemodialysis. *Am J Kidney Dis.* 2010;55(2):307-315.
- Fishbane S, Ford M, Fukagawa M, et al. A phase 3b, randomized, double-blind, placebo-controlled study of sodium zirconium cyclosilicate for reducing the incidence of predialysis hyperkalemia. *J Am Soc Nephrol.* 2019;30(9):1723-1733. doi: 10.1681/ASN.201905450.
- Floege J, Covic AC, Ketteler M, et al for the SuCroferric Oxyhydroxide Study Group. Long-term effects of the iron-based phosphate binder, suCroferric oxyhydroxide, in dialysis patients. *Nephrol Dial Transplant.* 2015;30(6):1037-1046.
- Floege J, Covic AC, Ketteler M, et al. A phase III study of the efficacy and safety of a novel iron-based phosphate binder in dialysis patients. *Kidney Int.* 2014;86(3):638-647.
- Food and Drug Administration Summary Review: Veltassa (patiromer). FDA/CDR resources page. Food and Drug Administration Web site. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/205739Orig1s000SumR.pdf. Accessed May 1, 2021.
- Fosrenol [package insert]. Lexington, MA: Takeda Pharmaceuticals USA, Inc.; August 2020.
- Frazão JM, Adragão T. Non-calcium-containing phosphate binders: comparing efficacy, safety, and other clinical effects. *Nephron Clin Pract.* 2012;120(2):c108-119.
- Hervas JG, Prados D, Cerezo S. Treatment of hyperphosphatemia with sevelamer hydrochloride in hemodialysis patients: a comparison with calcium acetate. *Kidney Int.* 2003;63(85):S69-72.
- Hollander-Rodriguez JC, Calvert JF Jr. Hyperkalemia. *Am Fam Physician.* 2006;73(2):283-290.
- Hutchison AJ, Barnett ME, Krause R, et al. Long-term efficacy and safety profile of lanthanum carbonate: results for up to 6 years of treatment. *Nephron Clin Pract.* 2008;110(1):c15-23.
- Hutchison AJ, Maes B, Vanwalleghem J, et al. Long-term efficacy and tolerability of lanthanum carbonate: results from a three-year study. *Nephron Clin Pract.* 2006;102(2):c61-71.
- Isakova T, Nickolas TL, Denburg M, et al. KDOQI US Commentary on the 2017 KDIGO Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Am J Kidney Dis.* 2017;70(6):737-751.
- Iwasaki Y, Takami H, Tani M, et al. Efficacy of combined sevelamer and calcium carbonate therapy for hyperphosphatemia in Japanese hemodialysis patients. *Ther Apher Dial.* 2005;9(4):347-351.
- Jamal SA, Vandermeer B, Raggi P, et al. Effect of calcium-based versus non-calcium-based phosphate binders on mortality in patients with chronic kidney disease: an updated systematic review and meta-analysis. *Lancet.* 2013;382(9900):1268-1277.
- Joy MS, Finn WF. Randomized, double-blind, placebo-controlled, dose-titration, Phase III study assessing the efficacy and tolerability of lanthanum carbonate: a new phosphate binder for the treatment of hyperphosphatemia. *Am J Kid Dis.* 2003;42(1):96-107.
- Kasai S, Sato K, Murata Y, et al. Randomized crossover study of the efficacy and safety of sevelamer hydrochloride and lanthanum carbonate in Japanese patients undergoing hemodialysis. *Ther Apher Dial.* 2012;16(4):341-349.
- Kestenbaum B, Sampson JN, Rudser KD, et al. Serum phosphate levels and mortality risk among people with chronic kidney disease. *J Am Soc Nephrol.* 2005;16(2):520-528.
- Ketteler M, Rix M, Fan S, et al. Efficacy and tolerability of sevelamer carbonate in hyperphosphatemic patients who have chronic kidney disease and are not on dialysis. *Clin J Am Soc Nephrol.* 2008;3(4):1125-1130.
- Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). *Kidney Int Suppl.* 2017;7:1-59.
- Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). *Kidney Int.* 2009;76(Suppl 113):S1-130.
- Kosiborod M, Rasmussen HS, Lavin P, et al. Effect of sodium zirconium cyclosilicate on potassium lowering for 28 days among outpatients with hyperkalemia: the HARMONIZE randomized clinical trial. *JAMA.* 2014;312(21):2223-2233.
- Kovesdy CP, Lu JL, Wall BM, et al. Changes with lanthanum carbonate, calcium acetate, and phosphorus restriction in CKD: a randomized controlled trial. *Kidney Int Rep.* 2018;3(4):897-904.
- Lepage L, Dufour AC, Doiron J, et al. Randomized clinical trial of sodium polystyrene sulfonate for the treatment of mild hyperkalemia in CKD. *Clin J Am Soc Nephrol.* 2015;10(12):2136-2142.
- Lewis JB, Sika M, Koury MJ, et al. Ferric citrate controls phosphorus and delivers iron in patients on dialysis. *J Am Soc Nephrol.* 2015;26:493-503.
- Lokelma [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; October 2020.
- Mehrotra R, Martin KJ, Fishbane S, et al. Higher strength lanthanum carbonate provides serum phosphorus control with a low tablet burden and is preferred by patients and physicians: a multicenter study. *Clin J Am Soc Nephrol.* 2008;3(5):1437-1445.
- Mount DB. Treatment and prevention of hyperkalemia in adults. UpToDate Web site. December 8, 2020. <http://www.uptodate.com>. Accessed May 1, 2021.
- Natale P, Palmer SC, Ruospo M, Saglimbene VM, Strippoli GF. Potassium binders for chronic hyperkalaemia in people with chronic kidney disease. *Cochrane Database Syst Rev.* 2020;26(6):CD013165. doi: 10.1002/14651858.CD013165.pub2.
- National Kidney Foundation. Best practices in managing hyperkalemia in chronic kidney disease. 2016. <https://www.kidney.org/sites/default/files/02-10-7259%20Hyperkalemia%20Tool.pdf>. Accessed May 1, 2021.
- National Kidney Foundation. KDOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis.* 2003;42(Suppl 3):S1-202.
- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations [database on the internet]. Silver Spring, MD: Food and Drug Administration (US) website; 2021. Available at: <http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>. Accessed May 1, 2021.
- Ouellet G, Cardinal H, Mailhot M, et al. Does concomitant administration of sevelamer and calcium carbonate modify the control of phosphatemia? *Ther Apher Dial.* 2009;14(2):172-177.
- Packham DK, Rasmussen HS, Lavin PT, et al. Sodium zirconium cyclosilicate in hyperkalemia. *N Engl J Med.* 2015;372(3):222-231.
- Patel L, Bernard LM, Elder GJ. Sevelamer versus calcium -based binders for treatment of hyperphosphatemia in CKD: a meta-analysis of randomized controlled trials. *Clin J Am Soc Nephrol.* 2016;11(2):232-244.

- Perry CM, Plosker GL. Sevelamer carbonate: a review in hyperphosphataemia in adults with chronic kidney disease. *Drugs*. 2014;74(7):771-792.
- PhosLo [package insert]. Waltham, MA: Fresenius Medical Care; March 2013.
- Phoslyra [package insert]. Waltham, MA: Fresenius Medical Care; September 2020.
- Pieper AK, Haffner D, Hoppe B, et al. A randomized crossover trial comparing sevelamer with calcium acetate in children with CKD. *Am J Kidney Dis*. 2006;47(4):625-635.
- Qunibi WY, Hootkins RE, McDowell LL, et al. Treatment of hyperphosphatemia in hemodialysis patients: the Calcium Acetate Renagel Evaluation (CARE Study). *Kidney Int*. 2004;65(5):1914-1926.
- Raebel MA. Hyperkalemia associated with use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. *Cardiovasc Ther*. 2012;30(3):e156-166.
- Rafique Z, Weir MR, Onuigbo M, et al. Expert panel recommendations for the identification and management of hyperkalemia and role of patiromer in patients with chronic kidney disease and heart failure. *J Manag Care Spec Pharm*. 2017;23(4-a Suppl):S10-s19. doi:10.18553/jmcp.2017.23.4-a.s10
- Renagel [package insert]. Cambridge, MA: Genzyme Corporation; April 2020.
- Renvela [package insert]. Cambridge, MA: Genzyme Corporation; April 2020.
- Roger SD, Lavin PT, Lerma EV, et al. Long-term safety and efficacy of sodium zirconium cyclosilicate for hyperkalemia in patients with mild/moderate versus severe/end-stage chronic kidney disease: comparative results from an open-label, phase 3 study. *Nephrol Dial Transplant*. 2021;36(1):137-150. doi: 10.1093/ndt/gfz285.
- Roger SD, Spinowitz BS, Lerma EV, et al. Efficacy and safety of sodium zirconium cyclosilicate for treatment of hyperkalemia: an 11-month open-label extension of HARMONIZE. *Am J Nephrol*. 2019;50(6):473-480. doi: 10.1159/000504078.
- Ruospo M, Palmer SC, Natale P, et al. Phosphate binders for preventing and treating chronic kidney disease –mineral and bone disorder (CKD-MBD). *Cochrane Database Syst Rev*. 2018;(8):CD006023.doi: 10.1002/14651858.CD006023.pub3.
- Shigematsu T. Lanthanum carbonate effectively controls serum phosphate without affecting serum calcium levels in patients undergoing hemodialysis. *Ther Apher Dial*. 2008;12(1):55-61.
- Shigematsu T. One year efficacy and safety of lanthanum carbonate for hyperphosphatemia in Japanese chronic kidney disease patients undergoing hemodialysis. *Ther Apher Dial*. 2010;14(1):12-19.
- Sodium polystyrene sulfonate powder for suspension [package insert]. Rahway, NJ: Sunrise Pharmaceutical, Inc.; March 2020.
- Sodium polystyrene sulfonate suspension [package insert]. Bridgewater, NJ: Trigen Laboratories, LLC; July 2017.
- Spinowitz BS, Fishbane S, Pergola PE, et al; ZS-005 Study Investigators. Sodium zirconium cyclosilicate among individuals with hyperkalemia: a 12-month phase 3 study. *Clin J Am Soc Nephrol*. 2019;14(6):798-809. doi: 10.2215/CJN.12651018.
- Sprague SM, Abboud H, Qiu P, et al. Lanthanum carbonate reduces phosphorus burden in patients with CKD Stages 3 and 4: a randomized trial. *Clin J Am Soc Nephrol*. 2009;4(1):178-185.
- St. Peter WL, Liu J, Weinhandl E, et al. A comparison of sevelamer and calcium-based phosphate binders on mortality, hospitalization, and morbidity in hemodialysis: a secondary analysis of the Dialysis Clinical Outcomes Revisited (DCOR) randomized trial using claims data. *Am J Kidney Dis*. 2008;51(3):445-454.
- Sterns RH, Rojas M, Bernstein P, Chennupati S. Ion-exchange resins for the treatment of hyperkalemia: are they safe and effective? *J Am Soc Nephrol*. 2010;21(5):733-735.
- Suki WN, Zabaneh R, Cangiano JL, et al. Effects of sevelamer and calcium-based phosphate binders on mortality in hemodialysis patients. *Kidney Int*. 2007;72(9):1130-1137.
- Umanath K, Jalal DI, Greco BA, et al for the Collaborative Group. Ferric citrate reduces intravenous iron and erythropoiesis-stimulating agent use in ESRD. *J Am Soc Nephrol*. 2015;26(10):2578-2587.
- Velphoro [package insert]. Waltham, MA: Fresenius Medical Care; February 2020.
- Veltassa [package insert]. Redwood City, CA: Relypsa, Inc.; May 2018.
- Voormolen N, Noordzij M, Grootendorst DC, et al. High plasma phosphate as a risk factor for decline in renal function and mortality in pre-dialysis patients. *Nephrol Dial Transplant*. 2007;22(10):2909–2916.
- Weir MR, Bakris GL, Bushinsky DA, et al; for the OPAL-HK Investigators. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. *N Engl J Med*. 2015;372(3):211-221.
- Wilson R, Zhang P, Smyth M, et al. Assessment of survival in a two-year comparative study of lanthanum carbonate vs standard therapy. *Curr Med Res Opin*. 2009;25(12):3021-3028.
- Wuthrich RP, Chonchol M, Covic A, et al. Randomized clinical trial of the iron-based phosphate binder PA21 in hemodialysis patients. *Clin J Am Soc Nephrol*. 2013;8(2):280-289.
- Zannad F, Hsu BG, Maeda Y, et al. Efficacy and safety of sodium zirconium cyclosilicate for hyperkalemia: the randomized, placebo-controlled HARMONIZE-Global study. *ESC Hear Fail*. 2020;7(1):54-64. doi: 10.1002/ehf2.12561.

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