PHARMACY AND THERAPEUTICS
FORMULARY CLASS EVALUATION--Summary

THERAPEUTIC CLASS:	Potassium Binding Agents
SIMILAR DRUGS:	Sodium polystyrene sulfonate (Kayexalate®, SPS®), Patiromer (Veltassa®), Sodium zirconium cyclosilicate (Lokelma®)[4]
REQUESTING PHYSICIAN:	Dr. Kumjian, Dr. Bazemore, Dr. Eskandar (Nephrology)
REASON FOR REVIEW:	Request for evaluation. New drug approval since most recent review.
DATE OF REQUEST:	November 2019
EXPECTED USE:	Frequent use in patients for the treatment of non-emergent hyperkalemia
RECOMMENDATION:	Recommend substituting sodium zirconium cyclosilicate for patiromer on our formulary and restrict sodium polystyrene sulfonate suspension to rectal use for patients unable to take oral medications.

NOTES OF INTEREST:

- Both sodium zirconium cyclosilicate and patiromer have demonstrated similar potassium reduction efficacy with fewer side effects than sodium polystyrene.
- Whereas patiromer has been shown to have more gastrointestinal side effects, sodium zirconium cyclosilicate contains sodium and has an increased risk for edema, which may restrict its use in certain patient populations.[9]
- Sodium zirconium cyclosilicate has the quickest onset of action in comparison to the other agents in its class and would be the most beneficial agent for acute (non-emergent) reduction in potassium.
- Sodium polystyrene sulfonate rectal suspension should be reserved for patients unable to take oral medications.

SAFETY ISSUES (MEDICATION ERROR POTENTIAL): Include only the items that have something listed.

- Sound alikes: Sodium polystyrene sulfonate (Kayexalate®): Potassium chloride (Kay Ciel®)
- Difficult/Unusual administration:
  Sodium polystyrene sulfonate:
  - Oral: Do not mix in potassium-containing fruit juice. Shake suspension well prior to administration. Powder for suspension must be mixed with water or syrup prior to administration.
  - Rectal: Administer cleaning edema prior to administration. Administer as a body temperature emulsion. Retain enema in colon for ≥ 30 minutes after administration. After retention time is complete, irrigate colon with a non sodium-containing solution to remove resin.[4,5]

  Sodium zirconium cyclosilicate:
- Empty entire contents of packets into a glass with ≥ 3 tablespoons of water. Stir well and drink immediately.
- Difficult/Unusual storage requirements:
  Patiromer: Refrigerate at 2 - 8 C
- Difficult/Unusual scheduling:
  Sodium polystyrene sulfonate:
  - Oral: Take other medications ≥ 3 hours before or after dose.

  Patiromer: Take other medications ≥ 3 hours before or after dose.[4,9]

  Sodium zirconium cyclosilicate: Administer other oral medications ≥ 2 hours before or after dose.[4,7]

COST ANALYSIS:

- *Sodium polystyrene sulfonate* (SPS, Kayexalate)
  - Suspension, oral 15 g/60 mL [$10.43 per 60 mL suspension]

- *Patiromer* (Veltassa)
  - 8.4 g [$25.79 per pack]
  - 16.8 g [$25.79 per pack]
  - 25.2 g [$25.79 per pack]

- *Sodium zirconium cyclosilicate* (Lokelma)
  - 5 g [$13.14 per pack]
  - 10 g [$13.14 per pack]

PHARMACY AND THERAPEUTICS
FORMULARY CLASS EVALUATION

THERAPEUTIC CLASS: Potassium Binding Agents

SIMILAR DRUGS: Sodium polystyrene sulfonate (Kayexalate®, SPS®), Patiromer (Veltassa®), Sodium zirconium cyclosilicate (Lokelma®)

REQUESTING PHYSICIAN: Dr. Kumjian, Dr. Bazemore, Dr. Eskandar (Nephrology)

REASON FOR REVIEW: Request for evaluation. New drug approval since most recent review.

DATE OF REQUEST: November 2019

EXPECTED USE: Frequent use in patients for the treatment of non-emergent hyperkalemia

RECOMMENDATION: Recommend substituting sodium zirconium cyclosilicate for patiromer on our formulary and restrict sodium polystyrene sulfonate suspension to rectal use for patients unable to take oral medications.

INDICATIONS:
Treatment of hyperkalemia - *Should not be used as an emergency treatment for life-threatening hyperkalemia due to delayed onset of action*[4]

EXPECTED PATIENT POPULATION:
Adult patients with hyperkalemia, most commonly caused by renal insufficiency, heart failure, and medications affecting the renin-angiotensin-aldosterone system, potassium-sparing diuretics, and nonsteroidal anti-inflammatory drugs. Although sometimes utilized in the pediatric population, safety and efficacy data have not yet been established in the pediatric population.[3,5,7,8]

CLINICAL PHARMACOLOGY:
Potassium is the second most-abundant cation in the body and performs various physiological functions, including cellular metabolism, macronutrient synthesis, and maintenance of electrical action potential across cellular membranes; however, hyperkalemia can cause alterations in neuromuscular and cardiac function.

- *Sodium polystyrene sulfonate* removes potassium by exchanging sodium ions for potassium ions within the intestines and increasing potassium excretion.
- *Patiromer* is a non-absorbed calcium-sorbitol polymer that binds potassium in the gastrointestinal lumen and increases fecal potassium excretion.
- *Sodium zirconium cyclosilicate* removes potassium by exchanging potassium for hydrogen and sodium within the gastrointestinal lumen and increasing potassium excretion.[2,4]

PHARMACOKINETICS:[4]

	Sodium polystyrene sulfonate	**Patiromer**	**Sodium zirconium cyclosilicate**
Absorption	Not systemically absorbed	Not systemically absorbed	Not systemically absorbed
Onset of action	Hours - days	7 hours	1 hour
Excretion	Feces	Feces	Feces

COMPARATIVE EFFICACY:
Sodium polystyrene sulfonate was FDA-approved in 1958 and was the only potassium binding agent until recent years. Recent clinical trials that demonstrate its efficacy in chronic hyperkalemia poorly support its use. They had small sample sizes, short study durations, and primarily patients with mild baseline hyperkalemia. Multiple studies have demonstrated that both patiromer and sodium zirconium cyclosilicate have statistically and clinically significant reductions in potassium. While these two agents have not been compared in a head-to-head trial, a meta-analysis, including two phase 2 studies and four phase 3 studies, compared efficacy of these two agents. For patiromer, there was a significant -0.36 mEq/L change in potassium at day 3 and -0.7 mEqL change in potassium at 4 weeks. Sodium zirconium cyclosilicate reduced potassium by -0.17 mEq/L at 1-hour and -0.67 mEq/L at 48 hours .[14] Overall, sodium zirconium cyclosilicate has the quickest onset of action and is the only potential agent for acute (non-emergent) reduction in potassium. Both sodium zirconium cyclosilicate and patiromer have demonstrated similar potassium reduction efficacy with fewer side effects than sodium polystyrene. Patiromer has been shown to have more gastrointestinal side effects, whereas, sodium zirconium cyclosilicate has an increased risk for edema which may restrict its use in sodium-sensitive patients (heart failure, hypertension, edema).[9]

Sodium polystyrene sulfonate:

Study	Description	Conclusion
Nasir, K. et al. (2014). Treatment of hyperkalemia in patients with chronic kidney disease: a comparison of calcium polystyrene sulphonate and sodium polystyrene sulphonate. *Journal of Ayub Medical College Abbottabad*, *26*(4), 455-8 Prospective, randomized, single-blind clinical trial	*Interventions:* SPS 5 g PO TID vs. CPS 5 g PO TID for 3 days *Patients: (n = 97)* Patients with CKD (Scr > 1.5 mg/dL) and hyperkalemia (> 5.2 mEq/L) *Primary outcome:* Mean change in potassium concentration over 3 days	The average potassium level decreased by 1.5 mEq/L in the SPS group and 1.0 mEq/L in the CPS group over 3 days, demonstrating that both agents could be used to treat hyperkalemia in CKD patients. The most common adverse events experienced by both groups were nausea, constipation, and anorexia. Due to the small sample size of this study, its results are supported with limited evidence.
Lepage, L et al. (2015). Randomized clinical trial of sodium polystyrene sulfonate for the treatment of mild hyperkalemia in CKD. *Clinical Journal of the American Society of Nephrology*, *10*(12), 2136-2142 Prospective, randomized, double-blind placebo-controlled clinical trial	*Interventions:* SPS 30 g PO once daily vs. placebo for 7 days *Patients: (n = 33)* Outpatients with CKD (eGFR < 40 mL/min) and mild hyperkalemia (5-5.9 mEq/L) *Primary outcome:* Mean change in potassium concentration from baseline to day 7	SPS was superior to placebo in the reduction of serum potassium with a mean difference of -1.04 mEq/L over 7 days. However, there were more electrolyte disturbances and gastrointestinal side effects in the SPS group. Due to the small sample size of this study, its results are supported with limited evidence.

SPS, sodium polystyrene sulfonate; CPS, calcium polystyrene sulfonate; CI, confidence interval

Patiromer:

Study	Description	Conclusion
Bushinsky, D. A. et al. (2015). Patiromer induces rapid and sustained potassium lowering in patients with chronic kidney disease and hyperkalemia. *Kidney international*, *88*(6), 1427-1433 Phase 1, prospective, open-label, single-arm clinical trial[1]	*Intervention:* Patiromer 8.4 g PO twice daily for 3 days *Patients: (n = 25)* Patients with CKD and hyperkalemia stabilized on RAASI *Primary outcome:* Change in potassium concentrations from baseline over 3 days	At 48 hours, there was a significant mean reduction in potassium by 0.75 mEq/L. Serum potassium did not increase before the next dose or for 24 hours after the last dose. Patiromer was well-tolerated, with mild constipation occurring in two patients.

Pitt, B et al. (2015). Effect of patiromer on reducing serum potassium and preventing recurrent hyperkalaemia in patients with heart failure and chronic kidney disease on RAAS inhibitors. *European journal of heart failure*, *17*(10), 1057-1065 OPAL-HK: Phase 3, prospective, single-blind, placebo-controlled withdrawal phase	*Intervention (Initial 4 -weeks):* Patiromer 4.2 g PO for mild hyperkalemia or 8.4 g PO for moderate to severe hyperkalemia twice daily *Patients (Initial 4 -weeks) (n = 243):* Patients with CKD stage 3 or and potassium concentration 5.1-6.5 mEq/L stabilized on RAASI *Primary outcome (Initial 4 -weeks):* Mean change in potassium concentrations from baseline to week 4 *Intervention (Randomized 8-weeks):* Continued patiromer at same dose received at week 4 or switched to placebo for 8 weeks *Patients (Randomized 8-weeks) (n = 107):* Patients with a potassium concentration of 3.8-5 mEq/L at the end of initial phase with potassium ≥ 5.5 mEq/L at baseline *Primary Outcome (Randomized 8-weeks):* Between-group difference in the median change in serum potassium level over first 4 weeks or to earliest visits when potassium was < 3.8 mEq/L or ≥ 5.5 mEq/L	*Initial 4-week phase:* There was an average -1.01 mEq/L reduction in potassium concentration at week 4 for both groups. *Randomized 8-weeks:* There was an increase in potassium by 0.72 mEq/L for placebo compared to no change in the patiromer group at week 8, demonstrating patiromer's sustained effects. Mild-moderate constipation was the most common adverse effect.

RAASI, renin-angiotensin-aldosterone system inhibitor

Sodium zirconium cyclosilicate:

Study	**Description**	**Conclusion**
Packham, D. K. et al. (2015). Sodium zirconium cyclosilicate in hyperkalemia. *New England Journal of Medicine*, *372*(3), 222-231 Phase 3, prospective, randomized, double-blind, placebo-controlled clinical trial	*Intervention (Initial phase):* ZS9 1.25 g, 2.5 g, 5 g, or 10 g PO three times daily with meals vs. placebo for 48 hours *Patients (Initial phase): (n = 753)* Ambulatory outpatients with hyperkalemia *Primary outcome (Initial phase)* Rate of change in mean potassium concentration compared to placebo over 48 hours *Intervention (Maintenance phase):* ZS9 dose from initial phase given once daily before breakfast or switched to placebo for days 3 to 14 *Patients (Maintenance phase):*	*Initial phase:* At 48 hours, the mean serum potassium level decreased by : 0.4 mEq/L with the 2.5 g 0.5 mEq/L with the 5 g 0.7 mEq/L with the 10 g The mean reduction from baseline at 1- hour after the first 10 g dose of ZS9 was - 0.11 mEq/L. All three doses of ZS9 demonstrated a significant reduction in serum potassium at 48 hours. In addition, the 10 g dose demonstrated a clinically significant effect within 1-hour of administration. *Maintenance phase:* During the 12 days of maintenance

	(n = 543) Ambulatory outpatients with normal potassium (3.5 - 4.9 mEq/L) hour 48 of initial phase *Primary outcome (Maintenance phase)* Mean potassium concentration compared to placebo over 12 days	therapy, both the 5 g and 10 g groups maintained serum potassium levels at 4.7 mEq/L and 4.5 mEq/L, respectively, demonstrating ZS9 ability to maintain normokalemia. Adverse effects were similar between the ZS9 and placebo group, with diarrhea being the most common adverse effect.
Kosiborod, M et al. (2014). Effect of sodium zirconium cyclosilicate on potassium lowering for 28 days among outpatients with hyperkalemia: the HARMONIZE randomized clinical trial. *Jama*, *312*(21), 2223-2233 HARMONIZE: Phase 3, prospective, randomized, double-blind, placebo-controlled clinical trial	*Intervention (Open-label phase):* ZS9 10 g PO three times daily with meals for 2 days *Patients (Open-label phase):* *(n = 258)* Ambulatory outpatients with hyperkalemia (≥5.1 mEq/L) *Primary outcome (Open-label phase):* Mean change in potassium concentrations over 48 hours *Intervention (Randomized phase):* ZS9 5 g, 10 g, or 15 g PO once daily vs. placebo for 28 days *Patients (Randomized phase):* *(n = 237)* Ambulatory outpatients with normal potassium (3.5-5 mEq/L) at hour 48 of initial phase *Primary outcome (Randomized phase):* Mean potassium concentration in each ZS9 group vs. placebo during days 8-29	*Open-label phase*: The mean reduction in serum potassium was - 1.1 mEq/L at 48 hours. A significant reduction in potassium by 0.2 mEq/L was noted at 1-hour compared to placebo. *Randomized phase*: At 28 days, the proportion of patients with mean potassium < 5.1 mEq/L was significantly higher in the ZS9 group (5 g: 80%, 10 g: 90%, 15 g: 94%) versus the placebo group (46%). Adverse events were comparable between the two groups, with edema more common in the 15 g group and hypokalemia more common in both the 10 g and 15 g groups.

ZS9, sodium zirconium cyclosilicate

CONTRAINDICATIONS:

- *Sodium polystyrene sulfonate*
  - Hypersensitivity to agents or any known components
  - Serum potassium < 5 mmol/L (excluding Kayexalate®)
  - Obstructive bowel disease
  - Neonates with reduced gut motility
  - Oral administration in neonates
  - Rectal administration of sorbitol-containing formulations in neonates[4,5]

- *Patiromer*
  - Hypersensitivity to agents or any known components[4,9]

- *Sodium zirconium cyclosilicate*
  - Hypersensitivity to agents or any known components

WARNINGS AND PRECAUTIONS:

- *Sodium polystyrene sulfonate*
  - Aspiration
  - Hypokalemia, hypomagnesmia, hypocalcemia
  - Fecal impaction
  - Gastrointestinal injury (including stenosis and ischemia)[4,5]
- *Patiromer*
  - Avoid use in patients with severe constipation, bowel obstruction or impaction, including abnormal post-operative motility disorders
  - May be ineffective in and may worsen gastrointestinal conditions
  - Hypomagnesmia[4,9]

- *Sodium zirconium cyclosilicate*
  - Edema (Each 5 gram dose of Lokelma® contains approximately 400 mg of sodium)
  - Avoid use in patients with severe constipation, bowel obstruction or impaction, including abnormal post-operative motility disorders
  - May be ineffective in and may worsen gastrointestinal conditions[4,7]

ADVERSE REACTIONS:

- *Sodium polystyrene sulfonate*: hypernatremia, hypocalcemia, hypokalemia, hypomagnesemia, gastrointestinal (constipation, flatulence, nausea, diarrhea)[4,5]

- *Patiromer*: hypomagnesemia, hypokalemia, gastrointestinal effects (constipation, flatulence, nausea, diarrhea)[4,9]

- *Sodium zirconium cyclosilicate*: edema, hypokalemia[4,7]

DRUG INTERACTIONS:

- *Sodium polystyrene sulfonate*
  - Avoid magnesium-containing laxatives due to increased risk for blood alkalinity/metabolic alkalosis
  - Avoid sorbitol (including meloxicam oral suspension) due to risk for colonic necrosis
  - May enhance adverse effects of aluminum hydroxide and increase the risk for intestinal obstruction
  - Antacids may enhance adverse effects of sodium polystyrene sulfonate and increase the risk for metabolic alkalosis
  - May increase serum concentration of digoxin
  - May decrease serum concentration of lithium, thyroid products, quetiapine, and iron preparations[4,5]

- *Patiromer* may decrease the serum concentration of ciprofloxacin, levothyroxine, and these medications should be administered 3 hours before or 3 hours after dose[4,9]

- *Sodium zirconium cyclosilicate* increases gastric pH which allows for medications that are weak acids (such as atorvastatin, furosemide, warfarin) to become more readily absorbed when given concomitantly.[4,7]

SAFETY ISSUES (MEDICATION ERROR POTENTIAL):

Sound alikes: Sodium polystyrene sulfonate (Kayexalate®): Potassium chloride (Kay Ciel®)

Difficult/Unusual administration:

- *Sodium polystyrene sulfonate*
  - Oral: Do not mix in potassium-containing fruit juice. Shake suspension well prior to administration. Powder for suspension must be mixed with water or syrup prior to administration.
  - Rectal: Administer cleaning edema prior to administration. Administer as a body temperature emulsion. Retain enema in colon for ≥ 30 minutes after administration. After retention time is complete, irrigate colon with a non-sodium-containing solution to remove resin.[4,5]
- *Sodium zirconium cyclosilicate*
  - Empty entire contents of packets into a glass with ≥ 3 tablespoons of water. Stir well and drink immediately.

Difficult/Unusual storage requirements:

- *Patiromer*: Refrigerate at 2 - 8 C

Difficult/Unusual scheduling:

- *Sodium polystyrene sulfonate*:
  - Oral: Take other medications ≥ 3 hours before or after dose.
- *Patiromer*: Take other medications ≥ 3 hours before or after dose.[4,9]
- *Sodium zirconium cyclosilicate*: Administer other oral medications ≥ 2 hours before or after dose.[4,7]

RECOMMENDED MONITORING:

- *Sodium polystyrene sulfonate*
  - Serum electrolytes (potassium, sodium, calcium, magnesium); ECG changes in select patients; signs/symptoms of fluid overload in sodium-sensitive patients (heart failure, hypertension, edema)[4,5]
- *Patiromer*
  - Serum potassium and magnesium[4,9]
- *Sodium zirconium cyclosilicate*
  - Serum potassium; signs/symptoms of edema[4,7]

DOSING:

- *Sodium polystyrene sulfonate*
  - Oral: 15 g 1 to 4 times daily
  - Rectal: 30-50g every 6 hours[4,5]

- *Patiromer*
  - Initial, oral: 8.4 g once daily; adjust dose at ≥ 1-week intervals in increments of 8.4 g
  - Maximum dose: 25.2 g/day[4,9]

- *Sodium zirconium cyclosilicate*
  - Initial, oral: 10 g three times daily for up to 48 hours; adjust dose by 5 g at 1-week intervals as needed based on potassium serum levels
  - Maintenance, oral: 10 g once daily (range: 5 g every other day to 15 g once daily)
  - Maximum maintenance dose: 15 g/day[4,7]

PRODUCT AVAILABILITY/COST ANALYSIS:

- *Sodium polystyrene sulfonate* (SPS, Kayexalate)
  - Suspension, oral 15 g/60 mL [$10.43 per 60 mL suspension]

- *Patiromer* (Veltassa)
  - 8.4 g [$25.79 per pack]
  - 16.8 g [$25.79 per pack]
  - 25.2 g [$25.79 per pack]

- *Sodium zirconium cyclosilicate* (Lokelma)
  - 5 g [$13.14 per pack]
  - 10 g [$13.14 per pack]

CONCLUSION:

Currently, both sodium polystyrene sulfonate and patiromer are on the St. Joseph's/Candler formulary. Both sodium zirconium cyclosilicate and patiromer have demonstrated similar potassium reduction efficacy with fewer side effects than sodium polystyrene. Whereas patiromer has been shown to have more gastrointestinal side effects, sodium zirconium cyclosilicate contains sodium and has an increased risk for edema, which may restrict its use in certain patient populations.[9] Sodium zirconium cyclosilicate has the quickest onset of action in comparison to the other agents in its class and would be the most beneficial agent for acute (non-emergent) reduction in potassium. We recommend substituting sodium zirconium cyclosilicate for patiromer on our formulary and reserving sodium polystyrene sulfonate rectal suspension for patients that unable to take oral medications.

References:

1. Bushinsky, D. A. et al. (2015). Patiromer induces rapid and sustained potassium lowering in patients with chronic kidney disease and hyperkalemia. *Kidney international*, *88*(6), 1427-1433
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10. Nasir, K. et al. (2014). Treatment of hyperkalemia in patients with chronic kidney disease: a comparison of calcium polystyrene sulphonate and sodium polystyrene sulphonate. *Journal of Ayub Medical College Abbottabad*, *26*(4), 455-8
11. Lepage, L et al. (2015). Randomized clinical trial of sodium polystyrene sulfonate for the treatment of mild hyperkalemia in CKD. *Clinical Journal of the American Society of Nephrology*, *10*(12), 2136-2142
12. Packham, D. K. et al. (2015). Sodium zirconium cyclosilicate in hyperkalemia. *New England Journal of Medicine*, *372*(3), 222-231
13. Pitt, B et al. (2015). Effect of patiromer on reducing serum potassium and preventing recurrent hyperkalaemia in patients with heart failure and chronic kidney disease on RAAS inhibitors. *European journal of heart failure*, *17*(10), 1057-1065
14. Meaney, C. et al. (2017). Systematic Review and Meta-Analysis of Patiromer and Sodium Zirconium Cyclosilicate: A New Armamentarium for the Treatment of Hyperkalemia. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, *37*(4), 401-411