

Drug Class Update with New Drug Evaluation: Potassium Exchangers

Date of Review: May 2019

Generic Name: Sodium Zirconium Cyclosilicate

End Date of Literature Search: 03/04/2019

Brand Name (Manufacturer): Lokelma™ (AstraZeneca)

Dossier Received: yes

Current Status of PDL Class:

See **Appendix 1**.

Purpose for Class Update:

Review new published data for management of hyperkalemia to help inform whether current Oregon Health Plan (OHP) policies remain appropriate for access to these medications. Review evidence for a new potassium binder, sodium zirconium cyclosilicate (SZC), recently approved by the United States (U.S.) Food and Drug Administration (FDA) for treatment of hyperkalemia in adults.

Research Questions:

1. Is there new evidence for differences in efficacy or harms between drug therapies (patiomer and sodium polystyrene sulfonate) used to treat hyperkalemia in adults?
2. What is the evidence for the safety and efficacy for SZC in treating hyperkalemia in adults?
3. Are there subgroups of patients based on demographics (e.g., age, racial groups, gender), comorbidities (e.g., drug-disease interactions, impaired renal function), or other medications (drug-drug interactions) for which SZC is more effective or safe?

Conclusions:

Comparative Evidence for Potassium Exchangers

- Two moderate quality systematic reviews evaluated published data regarding the safety and efficacy of patiomer and SZC in treating hyperkalemia.^{1,2} One systematic review summarized case reports of gastrointestinal events associated with the use of sodium polystyrene sulfonate (SPS).³
- The efficacy and safety of patiomer in hyperkalemic patients with heart failure or chronic kidney disease (CKD) was assessed in a 2018 systematic review and meta-analysis including 3 moderate quality studies.¹ There was a no statistically significant difference in all-cause mortality and serious cardiovascular events with patiomer compared to placebo (Risk Ratio (RR) 0.31; 95% (confidence interval) CI 0.03 to 2.90; p=0.30 and RR 3.5; 95% CI 0.40 to 30.27; p=0.26; respectively).¹ Patiomer lowered serum potassium concentrations more than placebo, and more patients developed hyperkalemia with placebo.¹
- A systematic review that compared efficacy and safety of patiomer and SZC in the treatment of hyperkalemia was published in 2017.² The meta-analysis of 3 moderate quality trials for patiomer showed a significant 0.70 mEq/L (95% CI 0.48 to 0.91 mEq/L) change in serum potassium at 4 weeks.² The meta-analysis of low quality data from 3 SZC trials found a significant change in potassium at 48 hours, of 0.67 mEq/L (95% CI 0.45 to 0.89 mEq/L).² Analysis of

pooled adverse effects from these trials indicates that patiromer was associated with more gastrointestinal upset and electrolyte depletion (hypomagnesemia), whereas SZC was associated more frequently with edema.²

- A 2013 systematic review evaluated case reports of gastrointestinal events associated with the use of SPS.³ The literature search identified 58 cases of adverse events related to SPS administration.³ The presenting gastrointestinal symptoms were abdominal pain and distension (n=33), gastrointestinal bleeding (n=13), diarrhea (n=10), and nausea and vomiting (n=6).³ Mortality was reported in 33% of these cases due to gastrointestinal injury.³

New Drug Evaluation: Sodium Zirconium Cyclosilicate

- The safety and efficacy of SZC in hyperkalemic outpatients was evaluated in two phase 3, randomized, double-blind, placebo-controlled trials of similar design.^{4,5}
- In Study 1 (ZS-003), patients with hyperkalemia who received SZC had a significant reduction in potassium levels at 48 hours compared with patients who received placebo, with normokalemia maintained during 12 days of maintenance therapy.⁴
- In the HARMONIZE trial, open-label SZC reduced serum potassium to normal levels within 48 hours in outpatients with hyperkalemia.⁵ Compared with placebo, 3 doses of SZC (5 gram, 10 grams and 15 grams) resulted in lower potassium levels and a higher proportion of patients with normal potassium levels for up to 28 days.⁵ In the randomized phase, serum potassium was significantly lower during days 8-29 with all 3 zirconium cyclosilicate doses versus placebo (4.8 mEq/L [95% CI, 4.6-4.9], 4.5 mEq/L [95% CI, 4.4-4.6], and 4.4 mEq/L [95% CI, 4.3-4.5] for 5 g, 10 g, and 15 g; 5.1 mEq/L [95% CI, 5.0-5.2] for placebo; P < 0.001 for all comparisons).⁵
- In both phase 3 clinical trials, SZC was well-tolerated and the incidence of adverse events was comparable between the active-treatment and placebo groups.^{4,5} In the HARMONIZE trial, SZC increased the incidence of edema in a dose-dependent manner (2%, 6%, and 14% for 5 gram, 10 gram, and 15 gram SZC doses versus 2% with placebo).⁵ Hypokalemia developed in 10% and 11% of the patients in the 10 gram and 15 gram SZC groups, versus none in the 5 gram or placebo groups.⁵ The hypokalemia resolved with dosage reduction or discontinuation of SZC.⁶
- There is insufficient evidence to evaluate the efficacy and safety of zirconium cyclosilicate beyond 4 weeks and to assess long-term clinical outcomes. Some patient groups that may benefit from potassium-lowering treatments, such as those receiving dialysis or hospitalized patients, were excluded from both trials.

Recommendations:

- Add sodium zirconium cyclosilicate to patiromer PA criteria to insure appropriate utilization for FDA-approved indications.
- Remove requirement for trial and failure of sodium polystyrene sulfonate because of its acute indication and FDA box warning.
- After evaluation of comparative costs in executive session to make patiromer non-preferred on the PDL. Maintain sodium zirconium cyclosilicate as non-preferred.

Summary of Prior Reviews and Current Policy

A new potassium binder, patiromer, was reviewed at the May 2016 Pharmacy and Therapeutics (P and T) Committee meeting. Low quality evidence demonstrates patiromer can decrease serum potassium levels from 0.35 mEq/L to 1.23mEq/L over 4 weeks of therapy in hyperkalemic patients with chronic kidney disease (CKD) on a renin angiotensin aldosterone system (RAAS) inhibitor. There is low quality evidence that in patients with CKD on a RAAS inhibitor with baseline hyperkalemia, patiromer is associated in a reduction in the recurrence of hyperkalemia (60% vs. 15%) through 8 weeks of treatment. The trials were short term and not designed to detect differences in any long term complications of chronic hyperkalemia (sudden cardiac death or ventricular arrhythmias). There is insufficient evidence that patiromer prevents long term complications, including arrhythmias. Due to the slow onset of patiromer, it is not recommended to be used in the acute treatment

of hyperkalemia (potassium ≥ 6.5 mEq/L).⁷ The phase 3 patiromer trials were short-term and not designed to detect differences in any long-term complications of chronic hyperkalemia (i.e., sudden cardiac death or ventricular arrhythmias). The recommendations were to defer Preferred Drug List (PDL) decisions until a review of sodium polystyrene sulfonate and SZC (which was awaiting FDA approval) could be presented at a future P and T meeting. Clinical PA criteria for patiromer were implemented to prevent its use in the emergent setting or in scenarios not supported by the medical literature.

Background:

Hyperkalemia is a potentially life-threatening metabolic disorder caused by inability of the kidneys to excrete potassium, impairment of the mechanisms that move potassium from the circulation into cells, or excessive production through oral intake.⁸ Potassium is primarily absorbed from the gastrointestinal tract via the small intestine and the kidneys regulate potassium excretion and reabsorption.⁹ Hyperkalemia is defined as a serum potassium concentration greater than 5.0 mEq per liter.¹⁰ While the definitions of mild, moderate, and severe hyperkalemia vary, severe hyperkalemia is most often defined as a serum potassium concentration greater than 6.5 mEq per liter or the presence of electrocardiographic changes resulting from an abnormal serum potassium concentration.¹⁰ Hyperkalemia is most often associated with impaired renal function, hyperglycemia, cell lysis (rhabdomyolysis or hemolysis) or acidosis. Medications such as nonsteroidal anti-inflammatory drugs (NSAIDs), cyclosporine, tacrolimus, eplerenone, spironolactone, angiotensin converting enzyme inhibitors (ACEIs) and angiotensin-II receptor blockers (ARBs) can cause hyperkalemia due to interference with the renin-angiotensin-aldosterone pathway. Other medications that can cause hyperkalemia include: azole antifungals, triamterene, amiloride, trimethoprim, digoxin, and beta blockers.¹¹ Hyperkalemia may lead to altered mental status, muscle weakness, paralysis, impaired renal acidification, or cardiac arrhythmias with fatal outcomes.¹¹

The incidence and prevalence of hyperkalemia in the general population is low (2–3%).¹² However, studies in patients with CKD have found higher frequencies of hyperkalemia, often as high as 40–50%, especially in diabetic patients, those with advanced stages of CKD, and heart failure patients treated with RAAS inhibitors.¹² Therapy for CKD and heart failure often includes RAAS inhibitors, and the administration of these medications may lead to increases in plasma potassium.¹³ Hyperkalemia has been reported to occur in approximately 10% of outpatients within a year of initiating an ACE inhibitor or ARB.¹⁴ Consequently, hyperkalemia may often lead to dose reduction or discontinuation of RAAS therapy, which in turn may lead to worsening of CKD or heart failure.

Acute management of hyperkalemia involves various interventions, including the intravenous administration of drugs that affect the cellular distribution of potassium and drugs that stabilize the myocardium, or definitive measures to remove potassium from the body.¹² Hemodialysis is an effective acute therapy for potassium removal from the body in an inpatient setting, but it is invasive and requires specialized equipment and personnel.¹² Medications used to manage acute hyperkalemia are described in **Table 1**.

Table 1. Medications for Treating Acute Hyperkalemia^{8,10}

Agent	Mechanism	Risks/Considerations
Intravenous insulin 10 units co-administered with intravenous dextrose (50%) 25 grams	Stimulates potassium uptake into cells	<ul style="list-style-type: none"> Does not permanently remove potassium from body Risk for hypoglycemia and electrolyte imbalances
Beta-adrenergic agonist (e.g., nebulized albuterol 10 -20 mg in 4 ml normal saline over 15 minutes)	Stimulates potassium uptake into cells	<ul style="list-style-type: none"> Does not permanently remove potassium from body Can precipitate tachycardia Inconsistent response May not be appropriate for use in patients with hypertension, heart failure, or tachyarrhythmia

Intravenous calcium gluconate (10%) or calcium chloride (10%) – 1 gram over 10 minutes	Protects against negative cardiac effects of potassium imbalance	<ul style="list-style-type: none"> • Does not affect potassium levels • Hypercalcemia • Can precipitate bradycardia and other arrhythmias • Can cause tissue damage • Contraindicated in patients taking digoxin
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Abbreviations: mg = milligram; ml = milliliters

Chronic management of hyperkalemia usually starts by identifying and eliminating correctable causes, such as a high potassium intake, hyperkalemia-inducing medications or metabolic acidosis.¹² Effective interventions include dietary education and a review of prescribed, over-the-counter and herbal medications.¹² In addition, loop diuretics and sodium bicarbonate can be administered.¹² Administration of aldosterone (in the form of oral fludrocortisone acetate) is effective in patients with aldosterone deficiency, but high doses might be needed, which can induce sodium retention, edema and hypertension.¹² Potassium binding resins such as SPS and patiomer are other therapeutic options.¹² Due to their delayed onset of action, SPS and patiomer should not be used as an emergency treatment for life-threatening hyperkalemia.^{7,15} **Table 2** provides an overview of the 3 FDA-approved potassium exchangers currently on the U.S. market.

Sodium polystyrene sulfonate binds potassium in the intestine and increases fecal potassium excretion, thereby reducing serum potassium concentrations. The FDA first approved SPS for the treatment of hyperkalemia in 1958, 4 years before passage of the Kefauver-Harris Drug Amendments, which require drug manufacturers to prove the effectiveness of their products before marketing them.¹⁶ No data from clinical trials of SPS are included in the SPS prescribing information.¹⁵ Sodium polystyrene sulfonate was studied in one small (n=33), short term (7 day), randomized controlled trial which demonstrated limited efficacy of SPS compared to placebo.¹⁷ In this study, patients with CKD and mild hyperkalemia (5.0 to 5.9 mEq/L) received either SPS 30 grams once daily or placebo. Although SPS was superior to placebo in the reduction of serum potassium (mean difference between groups, -1.04 mEq/L; 95% CI: -1.37 to -0.71), achieving normokalemia at the end of treatment was not statistically significantly different between treatment groups (73% SPS vs. 38% placebo, P=0.07).¹⁷ In 2009, the FDA issued a black box warning against the concomitant use of SPS and sorbitol due to the potential for dangerous GI side effects, including intestinal necrosis, bleeding, and ischemic colitis.¹⁵ Additional limitations of SPS use indicated in the prescribing information include risk of hypokalemia, hypernatremia, diarrhea, and gastrointestinal intolerance.¹⁵

Patiomer, a non-absorbed, potassium-binding polymer, exchanges calcium for potassium in the distal colon which promotes fecal potassium excretion.⁷ Patiomer binds to other orally administered medicines including ciprofloxacin, levothyroxine, and metformin. Therefore, administration of patiomer is recommended at least 6 hours before or after other oral medications.⁷ In clinical trials, hypomagnesemia was reported as an adverse reaction in 5.3% of patients treated with patiomer.⁷ The most common adverse event was constipation that led to patiomer discontinuation in 6–9% of patients.⁷ Patients are advised to avoid patiomer use if they have severe constipation, bowel obstruction, or impaction.⁷ Additionally, patiomer should be stored in the refrigerator at 2° to 8°C.⁷

Table 2. Medications FDA-Approved to Treat Non-Life-Threatening Hyperkalemia^{6,7,15}

Characteristic	Sodium Polystyrene Sulfonate	Patiomer	Sodium Zirconium Cyclosilicate
Brand Name	Kayexalate®	Veltassa®	Lokelma™
Year of FDA approval	1958	2015	2018
Site of Action	Colon	Colon	Entire gastrointestinal tract
Mechanism of Action	Exchanges potassium for sodium	Exchanges potassium for calcium	Exchanges potassium for sodium
Sodium Content	1.5 grams sodium per 15 gram dose	No sodium content	400 mg sodium per 5 gram dose

Sorbitol Content	20 grams sorbitol per 15 gram dose	4 grams sorbitol per 8.4 gram dose	No sorbitol content
Dose	Oral: 15 to 60 grams up to 4 times a day Rectal: 30 to 50 grams every 6 hours	Oral: 8.4 grams once a day with food, can be advanced up to 16.8 to 25.2 grams at weekly intervals	Oral: 10 grams three times a day for 48 hours followed by 10 grams once a day with food
Onset of Effect	2 to 6 hours	7 hours	1 hour
How Supplied	Light brown finely ground bulk powder	8.4, 16.8, and 2.5 2 gram packets	5 and 10 gram packets
Storage	Room temperature	Refrigerate; use within 3 months upon removal from refrigerator	Room temperature
Drug Interactions	Binds significantly to warfarin, metoprolol, phenytoin, furosemide, amlodipine, and amoxicillin. Administer at least 3 hours before or 3 hours after other oral medications.	May bind to orally administered medications and reduce their effectiveness; separate administration by 6 hours.	May increase concentrations of weakly acidic drugs such as furosemide and atorvastatin. May decrease the concentrations of weakly basic drugs such as dabigatran.
Safety Concerns	Colonic necrosis (case reports)	Hypomagnesemia (5.3%)	Edema 8-11% (dose dependent)

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

Efficacy and Safety of Patiromer in Hyperkalemia

The efficacy and safety of patiromer in hyperkalemic patients with heart failure or CKD was evaluated in a 2018 moderate quality systematic review and meta-analysis.¹ The literature search was conducted through 2015. Three moderate quality studies were included in the meta-analysis. Primary outcomes included: all-cause mortality, reduction in hospitalization, episodes of hypokalemia or hyperkalemia, and cardiovascular and gastrointestinal adverse events during the treatment period. There was a no statistically significant difference in all-cause mortality and serious cardiovascular events with patiromer compared to placebo (RR 0.31; 95% CI 0.03 to 2.90; p=0.30 and RR 3.5; 95% CI 0.40 to 30.27; p=0.26; respectively).¹ Hospitalization data were unavailable. Although serious gastrointestinal events were more common with placebo, there was a significant reduction (P=0.02) in the risk of non-serious gastrointestinal events with placebo (risk ratio=7.23; 95% CI 1.35 to 38.71).¹ Patiromer lowered serum potassium concentrations more than placebo, and more patients developed hyperkalemia with placebo.¹ The authors concluded that although patiromer seems promising in terms of efficacy and safety in multiple clinical trials, more RCTs with active comparator or existing standard of care in patients with established hyperkalemia are essential to come to a consensus about the indication and proper use of patiromer.¹

Systematic Review and Meta-Analysis of Patiromer and Sodium Zirconium Cyclosilicate

A moderate quality systematic review designed to compare efficacy and safety of patiromer and SZC in the treatment of hyperkalemia was published in 2017.² Significant heterogeneity was found in the meta-analysis with an I^2 value ranging from 80.6–99.6%.² The meta-analysis of 3 moderate quality trials for patiromer showed a significant 0.70 mEq/L (95% confidence interval [CI] 0.48 to 0.91 mEq/L) change in serum potassium at 4 weeks compared to baseline.² The meta-analysis of low quality data (due to the open label design of the initial run-in phase) from 3 SZC trials found a significant change in potassium at 48 hours, of 0.67 mEq/L (95% CI 0.45 to 0.89 mEq/L).² By 1 hour after SZC administration, change in potassium was 0.17 mEq/L (95% CI 0.05 to 0.30).² Analysis of pooled adverse effects from these trials indicates that patiromer was associated with more gastrointestinal upset (7.6% constipation, 4.5% diarrhea) and electrolyte depletion (7.1% hypomagnesemia), whereas SZC was associated with edema (0.9%).² Both agents exhibited statistically and clinically significant reductions in potassium for the primary end point of this meta-analysis.²

Safety of Sodium Polystyrene Sulfonate

A 2013 systematic review evaluated case reports of gastrointestinal events associated with the use of SPS.³ The literature search identified 58 cases of adverse events related to SPS administration.³ The presenting gastrointestinal symptoms were abdominal pain and distension (n=33), gastrointestinal bleeding (n=13), diarrhea (n=10), and nausea and vomiting (n=6).³ The median time from the first sodium polystyrene sulfonate dose to the presentation of gastrointestinal symptoms was 2 days (interquartile range, 1-5 days).³ The colon was the most commonly affected segment of the gastrointestinal tract (n=44) followed by the small intestine (n=12).³ Histopathologic findings associated with SPS use were necrosis of the bowel wall (n=36), ulceration (n=28), and perforation (n=5).³ All patients had histopathologic examination of affected gastrointestinal segments, which demonstrated SPS crystals in 90% of patients.³ For patients with gastrointestinal injury associated with SPS use, the overall mortality rate was 33%.³ Ninety-four percent of patients who died had colonic necrosis on biopsy.³ The authors conclude SPS use, both with and without sorbitol, may be associated with fatal gastrointestinal injury.³ The prescribing information for SPS has been modified to include warnings about serious gastrointestinal events (bleeding, ischemic colitis, perforation) associated with SPS administration.¹⁵ Use of SPS should be avoided in patients at risk for developing constipation or impaction (inflammatory bowel disease, vascular intestinal atherosclerosis, previous bowel resection, or bowel obstruction).¹⁵

After review, one systematic review was excluded due to poor quality (e.g., indirect network-meta analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).¹⁸

Guidelines: The National Institute for Health and Care Excellence (NICE) is currently in the process of developing guidance documents for the use of patiromer and SZC in treating hyperkalemia. Final publication of both documents is pending.

New FDA Safety Alerts: No new safety alerts have been identified.

NEW DRUG EVALUATION: Sodium Zirconium Cyclosilicate (Lokelma™)

See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Sodium zirconium cyclosilicate (SZC) is a non-absorbable compound that exchanges hydrogen and sodium ions for potassium in the gastrointestinal tract.⁶ It is FDA-approved to treat non-life threatening hyperkalemia in adults.⁶ The SZC new drug application was submitted to the FDA in 2015, but approval was delayed until 2018 due to facility inspection findings, drug-drug interaction liability, and outstanding labeling issues.¹⁹ Sodium zirconium cyclosilicate is supplied in individual powder packets containing 5 or 10 grams which must be reconstituted into an oral solution before administration. For initial treatment of hyperkalemia, the recommended dose is 10 grams administered three times a day for up to 48 hours.⁶ For continued treatment, the recommended dose is 10 grams once daily.⁶ The dose may be up-titrated based on the serum potassium level at intervals of 1-week or longer and in increments of 5 grams.⁶ The recommended maintenance dose ranges from 5 grams every other day to 15 grams once daily.⁶ Due to its delayed onset of action, SZC should not be used as emergency treatment for acute hyperkalemia.⁶

The efficacy of SZC in hyperkalemic outpatients was evaluated in two phase 3, randomized, double-blind, placebo-controlled trials of similar design.^{4,5} Study 1 (ZS-003) evaluated the effectiveness of SZC in lowering serum potassium in a two-phase, double-blind trial in patients with hyperkalemia (5 to 6.5 mEq/L). In the initial phase, 753 patients were randomized to receive one of four doses of SZC (1.25, 2.5, 5, 10 grams) or placebo, administered three times daily for the initial 48 hours with meals. All concomitant medications were kept constant throughout the study, including diuretic agents, RAAS inhibitors, and antidiabetic therapies. Approximately 67% of subjects were taking RAAS inhibitors.⁴ Enrolled subjects had heart failure (40%), CKD (75%) or diabetes (60%) in addition to hyperkalemia.⁴ No dietary restrictions were required; patients were instructed to continue their usual diet without any specified changes. Seventy-two percent of patients (n=543) who achieved a potassium level between 3.5 and 5 mEq/L after receiving SZC during the acute phase were re-randomized to receive either their original SZC treatment dose or placebo once daily with breakfast from days 3 to 14.⁴ Patients assigned to the placebo group in the initial phase were randomly assigned to receive either SZC 1.25 grams or 2.5 grams in the maintenance phase.⁴ Study drug dose adjustment during the study was not permitted.

The primary endpoint in the initial phase was the difference in the exponential rate of change in serum potassium levels during the initial 48 hours of the study, comparing placebo-treated patients versus SZC-treated patients.⁴ The investigators felt the exponential rate of change was a more clinically relevant end point than the absolute change from baseline, since it includes the time to onset and incorporates all potassium measurements throughout the initial 48 hours.⁴ At 48 hours, the mean exponential rates of change from baseline per hour were reductions of 0.11% in the group receiving SZC 1.25 grams, 0.16% in the group receiving SZC 2.5 grams, 0.21% in the group receiving SZC 5 grams and 0.30% in the group receiving SZC 10 g, as compared with a reduction of 0.09% per hour in the placebo group (P<0.001 for the comparison with the three highest-dose groups; P>0.05 for the comparison with the 1.25-gram group).⁴ The primary endpoint in the maintenance phase was the mean exponential rate of change in the mean serum potassium levels over the 12-day treatment interval, comparing patients receiving SZC versus those receiving placebo.⁴ The mean exponential rate of change was an increase of 0.14% per hour in the group receiving SZC 10 grams versus 1.04% per hour in the respective placebo group (P<0.001), and an increase of 0.09% per hour with patients receiving SZC 5 grams versus 0.47% per hour with placebo (P = 0.008).⁴ The mean exponential rate of change with the 1.25 gram and 2.5 gram doses of SZC did not differ significantly from the rates with placebo and specific rates were not reported.⁴

The second trial (HARMONIZE), was a double-blind, two-phase trial evaluating SZC in hyperkalemic outpatients (K > 5.1 mEq/L). Baseline characteristics in this trial were similar to Study 1.⁵ Two hundred fifty-eight adult patients entered a 48-hour, open-label run-in period during which they received 10 gm of SZC three times daily for a total of 6 doses. A significant change in potassium (-0.2 mEq/L; 95% CI, -0.3 to -0.2; P<0.001) was noted 1 hour after the first 10-gm dose compared with baseline.⁵ In the initial open-label phase, a mean reduction of -1.1 mEq/L (95% CI: -1.1 to -1.0 mEq/L, P<0.001) in serum potassium was noted from baseline to 48 hours; the proportion of patients achieving normokalemia at 48 hours was 98%.⁵

Ninety-two percent of patients achieving normokalemia (3.5-5.0 mEq/L) in the open label phase were then randomized 4:4:4:7 to receive SZC, 5 g (n = 45 patients), 10 g (n = 51), or 15 g (n = 56), or placebo (n = 85) daily for 28 days.⁵ Reasons for not entering the maintenance phase included hypokalemia, hyperkalemia, and withdrawal of consent.⁵ If a patient's potassium value was between 3.0 and 3.4 mEq/L at any time during the randomized phase, the dose was reduced from once daily to every other day for the remainder of the study.⁵ The primary endpoint in the randomized withdrawal phase was the mean serum potassium value during days 8 to 29 in each SZC-treated group versus placebo. In the randomized phase, serum potassium was significantly lower during days 8-29 with all 3 zirconium cyclosilicate doses versus placebo (4.8 mEq/L [95% CI, 4.6-4.9], 4.5 mEq/L [95% CI, 4.4-4.6], and 4.4 mEq/L [95% CI, 4.3-4.5] for 5 g, 10 g, and 15 g; 5.1 mEq/L [95% CI, 5.0-5.2] for placebo; P < .001 for all comparisons).⁵ Refer to the comparative evidence table (**Table 5**) for more details about each trial.

Study Limitations:

In the Study 1 (ZS-003), the mean exponential rates of change with the 4 SZC doses were only compared to placebo, not to each other. Study 1 was not appropriately powered to detect the adverse event of hypokalemia. The HARMONIZE trial included an initial open-label, run-in phase which was not double blinded. Both trials were of short duration (12 to 28 days), and clinical outcomes other than potassium levels were not assessed. Some patient groups that may benefit from potassium-lowering treatments, such as those receiving dialysis or hospitalized patients, were excluded from both trials. The dosage of the RAAS inhibitor and duration of time patients had been receiving RAAS inhibitor before study entry were not noted in either trial. Other medications that may have an effect on serum potassium, such as diuretics and aldosterone antagonists, were not assessed. Finally, although the numbers of patients with conditions commonly associated with hyperkalemia were noted, the authors did not state how many patients had more than one of the associated concomitant conditions. Further studies are needed to evaluate the efficacy and safety of zirconium cyclosilicate beyond 4 weeks and to assess long-term clinical outcomes.

Clinical Safety:

In both phase 3 clinical trials, SZC was well-tolerated and the incidence of adverse events was comparable between the active-treatment and placebo groups.^{4,5} In the HARMONIZE trial, SZC increased the incidence of edema in a dose-dependent manner (2%, 6%, and 14% for 5 gram, 10 gram, and 15 gram SZC doses versus 2% with placebo).⁵ Each 5 gm dose of SZC contains 400 mg of sodium; therefore, edema appears to be related to the sodium load administered. The incidence of edema compiled by the manufacturer from all clinical trials is summarized in **Table 3**. The clinical importance of SZC-inducible sodium retention, particularly in susceptible patients with heart failure or CKD, remains to be determined in ongoing trials. In the HARMONIZE trial, hypokalemia developed in 10% and 11% of the patients in the 10-g and 15-g zirconium cyclosilicate groups, versus none in the 5-g or placebo groups.⁵ The hypokalemia resolved with dosage reduction or discontinuation of SZC.⁶

Table 3. Incidence of edema in clinical trials⁶

Adverse Event	Placebo	5 gm	10 gm	15 gm
Edema	2.4%	4.4%	5.9%	16.1%

Sodium zirconium cyclosilicate can temporarily increase gastric pH, which may alter the absorption of co-administered drugs with acid-dependent solubility, such as some azole antifungals and antiretroviral drugs.⁶ Therefore, the manufacturer recommends that oral medications with acid dependent solubility should not be taken within 2 hours of SZC.⁶

Look-alike / Sound-alike Error Risk Potential: No medications identified.

Comparative Endpoints:

Clinically Meaningful Endpoints:

- 1) Serum potassium levels
- 2) Symptoms related to hyperkalemia: i.e. cardiac arrhythmias
- 3) Time to serum potassium normalization
- 4) Adverse event rates
- 5) Serious adverse events
- 6) Study withdrawal due to an adverse event

Primary Study Endpoints:

- 1) Exponential rate of change in potassium levels at 48 hours
- 2) Mean serum potassium level during the 12 days of treatment
- 3) Mean serum potassium level during days 8-29 of treatment

Table 4. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	Exchanges sodium ions for potassium in the gastrointestinal tract which increases fecal potassium excretion and reduces serum potassium.
Oral Bioavailability	Not absorbed
Distribution and Protein Binding	N/A, not absorbed
Elimination	Fecal
Half-Life	N/A, not absorbed
Metabolism	N/A, not absorbed

Abbreviations: N/A = not available

Table 5. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Packham et al. ⁴ MC, MP, DB, PC, RCT 2 Phase Trial: Initial Phase	Initial Phase (2 days): 1. SZC 1.25 gm 2. SZC 2.5 gm 3. SZC 5 gm 4. SZC 10 gm 5. Placebo	<u>Demographics:</u> 1. Mean baseline serum potassium level=5.3 mEq/L 2. Mean age - 65 yo 3. Gender - 60% men 4. Race - 86% Caucasian	<u>Initial Phase:</u> 1. 154 2. 141 3. 157 4. 143 5. 158	<u>Primary Endpoint:</u> Initial Phase: Mean exponential rate of change in the mean serum potassium level from baseline at 48 hours 1. 0.11% per hour 2. 0.16% per hour 3. 0.21% per hour 4. 0.3% per hour		<u>Initial Phase:</u> <u>Any AE</u> 1. 16.2% 2. 9.2% 3. 14% 4. 11.9% 5. 10.8%	NA for all	Risk of Bias (low/high/unclear): <u>Selection Bias:</u> Low. Patients were randomized 1:1:1:1:1 to one of 5 groups in both phases. Baseline demographics similar between groups. Randomization was blinded and conducted by a third party not associated with clinical management of the study.

<p>over 48 hours followed by Maintenance Phase over 12 days</p> <p>N=753</p>	<p>Administered three times a day with meals for 48 hours</p> <p>Maintenance Phase (12 days):</p> <ol style="list-style-type: none"> SZC 1.25 gm SZC 2.5 gm SZC 5 gm SZC 10 gm Placebo <p>Administered once daily on days 3 to 14</p>	<ol style="list-style-type: none"> Percent with eGFR < 60 mL/min - 75% Taking RAASi - 67% Diabetic - 60% Percent with HF - 40% <p><u>Key Inclusion Criteria:</u></p> <ol style="list-style-type: none"> Adults over 18 years of age with a serum potassium level 5.0 to 6.5 mEq/L with the ability to undergo repeated blood draws <p><u>Key Exclusion Criteria:</u></p> <ol style="list-style-type: none"> Patients on dialysis Insulin-dependent diabetics Subjects with cardiac arrhythmias needing immediate treatment Participation in another clinical trial within 30 days Potassium level > 6.5 mEq/L Subjects with life expectancy of less than 3 months 	<p>Maintenance Phase:</p> <p><u>ITT:</u></p> <ol style="list-style-type: none"> 49 54 65 63 216 <p><u>PP:</u></p> <ol style="list-style-type: none"> 48 52 59 61 205 <p>Maintenance Phase</p> <p><u>Attrition:</u></p> <ol style="list-style-type: none"> 1% 1% 1% 1% 5% 	<p>5. 0.09 per hour</p> <p>1 vs. 5: p>0.05 All other groups vs. 5: p<0.001</p> <p><u>Secondary Endpoints:</u></p> <p>Initial Phase: Mean Serum Potassium at 48 hours</p> <ol style="list-style-type: none"> 5.1 mmol/L 4.9 mmol/L 4.8 mmol/L 4.6 mmol/L 5.3 mmol/L <p>MR = -0.25 mmol/L (95% CI -0.32 to -0.19)</p> <p>1 vs. 5: MR 0.3 mmol/L; NS 2 vs. 5: MR: -0.46 mmol/L (95% CI -0.53 to -0.39) p<0.001 3 vs. 5: MR: -0.54 mmol/L (95% CI -0.62 to -0.47) p<0.001 4 vs. 5: MR: 0.73 mmol/L (95% CI -0.82 to -0.65) p<0.001</p> <p><u>Maintenance phase:</u></p> <p>Mean exponential rate of change in the mean serum potassium level over 12-day treatment interval.</p> <ol style="list-style-type: none"> NR NR 0.09% per hour 0.14% per hour 0.47% per hour (5 gm comparator) and 1.04% per hour (10 gm comparator group) <p>1 vs. 5: NS 2 vs. 5: NS 3 vs. 5: P=0.008 4 vs. 5: P<0.001</p> <p>Mean serum potassium level during the 12-day treatment interval.</p> <ol style="list-style-type: none"> NR 	<p>NS NA</p> <p>NS NA</p> <p>NA</p> <p>NS NS NA NA</p>	<p><u>Gastrointestinal Disorder</u></p> <ol style="list-style-type: none"> 4.5% 2.1% 3.8% 3.5% 5.1% <p><u>Cardiac Disorder</u></p> <ol style="list-style-type: none"> 0.6% 0% 1.9% 1.4% 0% <p><u>Hypokalemia</u></p> <ol style="list-style-type: none"> 0% 0% 0% 0% <p>Maintenance Phase:</p> <p><u>Any AE</u></p> <ol style="list-style-type: none"> 25% 22% 22% 33% 25% <p><u>Gastrointestinal Disorder</u></p> <ol style="list-style-type: none"> 4% 6% 7% 5% 4% <p><u>Cardiac Disorder</u></p> <ol style="list-style-type: none"> 0% 0.9% 3.1% 3.2% 0.9% 	<p><u>Performance Bias:</u> Low. First 2 doses of SZC in the initial phase were administered at the study site and subsequent doses were administered as an outpatient. Placebo and SZC were identical in appearance.</p> <p><u>Detection Bias:</u> Low. Potassium levels sent to a central laboratory for analysis and verification.</p> <p><u>Attrition Bias:</u> Low. Attrition rates were similar in all study arms. Reasons for withdrawal were similar across all arms.</p> <p><u>Reporting Bias:</u> Low. Study protocol available online. All pre-specified primary and secondary outcomes reported.</p> <p><u>Other Bias:</u> High. ZS Pharma had a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. Primary author served as a consultant for ZS Pharmacy. One author is an employee of ZS Pharma. Six authors have received grant support from ZS Pharma or served on advisory boards for ZS Pharma.</p> <p>Applicability:</p> <p><u>Patient:</u> Included broad representation of patients in outpatient setting with hyperkalemia. Patients on dialysis, inpatients, or K >6.5 were excluded from this trial, so conclusions about safety or efficacy cannot be drawn in these populations.</p> <p><u>Intervention:</u> This was a dose finding trial.</p> <p><u>Comparator:</u> Placebo used as a comparator. Another resin (SPS or patiromer) would have provided reasonable comparative efficacy.</p> <p><u>Outcomes:</u> Potassium levels are reasonable to assess hyperkalemia. SZC doses only compared to placebo, not to each other.</p> <p><u>Setting:</u> 65 sites in the United States, Australia and South Africa</p>
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				<p>2. NR 3. 4.7mmol/L 4. 4.5 mmol/L 5. > 5.0 mmol/L</p> <p>1 or 2 vs. 5: NS 3 or 4 vs. 5: P<0.001</p>	<p>NS NA</p>	<p>95% CI and p values NR for all outcomes</p>	
<p>2. Kosiborod et al.⁵</p> <p>MC, MP, DB, PC, RCT</p> <p>2 phases: 258 subjects in the Initial OL Phase. Followed by 237 subjects with potassium level 3.5 to 5.0 randomized to the PC Maintenance Phase</p> <p>N=258</p>	<p>Initial OL Phase (2 days): 1.SZC 10 gm three times a day with meals for 48 hours (6 doses)</p> <p>Maintenance PC Phase (28 days): 1. SZC 5 gm once daily 2. SZC 10 gm once daily 3. SZC 15 gm once daily 4.Placbo once daily</p>	<p>Demographics: 1. Mean baseline serum potassium level=5.6 meq/L 2. Mean age - 64 yo 3. Gender - 58% men 4. Race - 83% Caucasian 5. Percent with eGFR < 60 ml/min - 66% 6. Taking RAAs - 70% 7. Diabetic - 66% 8.Percent with HF - 36%</p> <p>Key Inclusion Criteria: 1. Ambulatory patients over 18 yo with a potassium level ≥ 5.1 mEq/L with the ability to have repeated blood draws</p> <p>Key Exclusion Criteria: 1. Pseudohyperkalemia signs and symptoms 2. Subjects treated with lactulose, Xifaxan, or other non-absorbed antibiotics for hyperammonemia within 7 days of enrollment 3. Subjects treated with resins: sevelamer, SPS, calcium acetate, calcium carbonate or lanthanum within 7 days of study enrollment</p>	<p>Initial Phase: 1. 258</p> <p>Maintenance Phase: ITT : 1. 45 2. 51 3. 56 4. 85</p> <p>PP: 1. 40 2. 44 3. 49 4. 75</p> <p>Attrition during maintenance phase: 1. 5 (11%) 2. 7 (14%) 3. 7 (13%) 4. 10 (12%)</p>	<p>Primary Endpoint: Mean serum potassium level in each study group during days 8-29 of the randomized phase</p> <p>1. 4.8 meq/L (95% CI 4.6 to 4.9) 2. 4.5 meq/L (95% CI 4.4 to 4.6) 3. 4.4 meq/L (95% CI 4.3 to 4.5) 4. 5.1 meq/L (95% CI 5.0 to 5.2)</p> <p>1 vs. 4: MR = 0.3 meq/L; P<0.001 2 vs. 4: MR = 0.6 meq/L; P<0.001 3 vs. 4: MR = 0.7 meq/L; P<0.001</p> <p>Secondary Endpoints: Proportion of patients who were normokalemic (3.5–5 meq/L) on day 29</p> <p>1. 71%; p=0.01 vs. 4 2. 76%; p=0.002 vs. 4 3. 85%; p<0.001 vs. 4 4. 48%</p>	<p>NA NA NA</p> <p>23/5 28/4 37/3</p>	<p>Maintenance Phase SAE's: 1. 11% 2. 4% 3. 5% 4. 0%</p> <p>Gastrointestinal: 1. 0% 2. 2% 3. 2% 4. 7%</p> <p>Edema: 1. 2% 2. 6% 3. 14% 4. 2%</p> <p>Hypokalemia: (K<3.5 meq/L) 1. 0% 2. 10% 3. 11% 4. 0%</p> <p>95% CI and p values NR for all outcomes</p>	<p>Risk of Bias (low/high/unclear): Selection Bias: Unclear due to OL phase. OL phase followed by maintenance phase in which subjects were randomized 4:4:4:7 in a double blind manner. Weekly kits containing 8 boxes with 3 sachets of SZC per box were assigned via an IVRS/IWRS. Baseline demographics similar between groups. Performance Bias: Low. Oral placebo powder had the exact same appearance, taste, odor, and mode of administration as SZC. The first dose was administered in the clinic so staff could train the subject how to reconstitute the product for oral administration. Subsequent doses were administered as an outpatient. Detection Bias: Low. Assessments completed by Independent Data Monitoring Committee. Potassium levels sent to a central laboratory for analysis and verification. Attrition Bias: Low. Attrition rates were similar in all study arms. Reasons for withdrawal due to adherence, adverse events, and hypo- or hyperkalemia were similar across all arms. Reporting Bias: Low. ITT analysis which included patients who discontinued study, but had at least 1 follow-up potassium level. Other Bias: Unclear. Sponsored by ZS Pharma, Inc. Two investigators who participated trial had financial interests or arrangements > \$50,000 to disclose.</p> <p>Applicability: Patient: Included broad representation of patients in outpatient setting with hyperkalemia. Patients on dialysis, inpatients, or K >6.5 were excluded from this trial, so</p>

		<p>4. Patients on dialysis or with cardiac arrhythmias</p> <p>5. Potassium level > 6.5 mEq/L</p> <p>6. Subjects with life expectancy of less than 3 months</p>					<p>conclusions about safety or efficacy cannot be drawn in these populations.</p> <p><u>Intervention</u>: OL dose of 10 gm TID was based on a dose finding from Study 1. Maintenance phase dosing (10 gm and 15 gm) was also based on data from Study 1. 5 gm dose included to establish a minimum effective dose.</p> <p><u>Comparator</u>: Placebo. Direct comparison with patiromer or SPS would be helpful for comparative efficacy.</p> <p><u>Outcomes</u>: Potassium levels reasonable to assess hyperkalemia. SZC doses only compared to placebo, not to each other.</p> <p><u>Setting</u>: 44 sites in United States (80%), Australia (8%), and South Africa (12%)</p>
<p>Abbreviations [alphabetical order]: ARR = absolute risk reduction; CI = confidence interval; DB = Double-blind; DM = diabetes mellitus; GFR = estimated glomerular filtration rate; gm = gram; HF = Heart Failure; ITT = intention to treat; IVRS/IWRS = Interactive Voice/Web Response System; L = liter; MR = mean reduction compared to baseline; meq = milliequivalents; mITT = modified intention to treat; mmol = Millimole; MC = Multi-Center; MP = Multi-Phase; N = number of subjects; NA = not applicable; NR = Not Reported; NNH = number needed to harm; NNT = number needed to treat; OL = Open Label; PC = Placebo-controlled; PP = per protocol; RAAIs = Renin-Angiotensin-Aldosterone Inhibitors; RCT = Randomized Controlled Trial; SAE = Serious Adverse Events; SPS = sodium polystyrene sulfonate; SZC = sodium zirconium cyclosilicate; yo = years old</p>							

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Appendix 1: Current Preferred Drug List

Generic	Brand	Formulation	Route	PDL
patiomer calcium sorbitex	VELTASSA	POWD PACK	ORAL	
sodium polystyrene sulfon/sorb	KIONEX	ORAL SUSP	ORAL	N
sodium polystyrene sulfon/sorb	SPS	ORAL SUSP	ORAL	N
sodium polystyrene sulfon/sorb	SPS	ENEMA	RECTAL	N
sodium zirconium cyclosilicate	LOKELMA	POWD PACK	ORAL	

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to February Week 4 2019, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations March 04, 2019

1. Hyperkalemia/ 2658
2. Cation Exchange Resins/ 890
3. Sodium polystyrene sulfonate.mp. 195
4. Patiomer.mp. 93
5. Sodium zirconium cyclosilicate.mp. 43
6. 2 or 3 or 4 or 5 1121
7. 1 and 6 152
8. limit 7 to (english language and humans and "all adult (19 plus years)" and (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or comparative study or controlled clinical trial or meta-analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")) 15

Appendix 3: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **LOKELMA™** safely and effectively. See full prescribing information for **LOKELMA™**.

LOKELMA™ (sodium zirconium cyclosilicate) for oral suspension
Initial U.S. Approval: [2018]

INDICATIONS AND USAGE

LOKELMA is a potassium binder indicated for the treatment of hyperkalemia in adults. (1)

Limitation of Use

LOKELMA should not be used as an emergency treatment for life-threatening hyperkalemia because of its delayed onset of action. (1)

DOSAGE AND ADMINISTRATION

- Recommended starting dose is 10 g administered three times a day for up to 48 hours. (2.1)
- For maintenance treatment, recommended dose is 10 g once daily. (2.1)
- Adjust dose at one-week intervals as needed (by 5 g daily) to obtain desired serum potassium target range. (2.1)

DOSAGE FORMS AND STRENGTHS

- For oral suspension: 5 g per packet (3)

- For oral suspension: 10 g per packet (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Gastrointestinal Adverse Events in Patients with Motility Disorders. (5.1)
- Edema. (5.2)

ADVERSE REACTIONS

Most common adverse reactions with LOKELMA: mild to moderate edema. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

In general, other oral medications should be administered at least 2 hours before or 2 hours after LOKELMA. (2.2, 7, 12.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 5/2018

Appendix 4: Key Inclusion Criteria

Population	Adults with hyperkalemia
Intervention	Sodium zirconium cyclosilicate, patiromer, sodium polystyrene sulfonate
Comparator	Placebo
Outcomes	Rate of potassium reduction, mean serum potassium level
Timing	48 hours, 12 days, and 28 days
Setting	Outpatient

Patiromer and Sodium Zirconium Cyclosilicate

Goals:

- Restrict use of patiromer and sodium zirconium cyclosilicate (SZC) to patients with persistent or recurrent hyperkalemia not requiring urgent treatment.
- Prevent use in the emergent setting or in scenarios not supported by the medical literature.

Length of Authorization:

- 3 months

Requires PA:

- Patiromer and Sodium Zirconium Cyclosilicate

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. Is this a request for continuation of therapy previously approved by the FFS program (patient already on patiromer or Sodium Zirconium Cyclosilicate (SZC))?	Yes: Go to Renewal Criteria	No: Go to #2
2. What diagnosis is being treated?	Record ICD10 code. Go to #3	
3. Does the patient have persistent or recurrent serum potassium of ≥ 5.5 mEq/L despite a review for discontinuation of medications that may contribute to hyperkalemia (e.g., potassium supplements, potassium-sparing diuretics, nonsteroidal anti-inflammatory drugs)?	Yes: Go to #4	No: Pass to RPh. Deny; medical appropriateness
4. Does the patient have hyperkalemia requiring emergency intervention (serum potassium ≥ 6.5 mEq/L)?	Yes: Pass to RPh. Deny; medical appropriateness	No: Go to #5

Approval Criteria		
5. Is the request for patiomer?	Yes: Go to #6	No: Go to #7
6. Does the patient have hypomagnesemia (serum magnesium < 1.4 mg/dL)?	Yes: Pass to RPh. Deny; medical appropriateness	No: Go to #7
7. Does the patient have a severe GI disorder (i.e., major GI surgery (e.g., large bowel resection), bowel obstruction/impaction, swallowing disorders, gastroparesis, or severe constipation)?	Yes: Pass to RPh. Deny; medical appropriateness	No: Approve up to 3 months

Renewal Criteria		
1. Is the patient's potassium level < 5.1 mEq/L and has this decreased by at least 0.35 mEq/L from baseline?	Yes: Approve for up to 3 months	No: Pass to RPh. Deny; medical appropriateness

P&T Review: 05/19 (DM), 05/16
 Implementation: 7/1/2019, 8/16, 7/1/16