Drug Use Research & Management Program
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New Drug Evaluation: patiromer powder for oral suspension

Date of Review: 3/17/16
Generic Name: patiromer
PDL Class: Potassium Exchangers

End Date of Literature Search: 3/17/16
Brand Name (Manufacturer): Veltassa® (Relypsa)
AMCP Dossier Received: Yes

Research Questions:

- Is patiromer more effective than placebo at maintaining normal potassium levels in patients with chronic kidney disease (CKD) and patients with heart failure (HF) who are also on ACEIs, ARBs or spironolactone?
- Are there subgroups of patients based on demographics (e.g., age, racial groups, gender), comorbidities (e.g., drug-disease interactions, obesity), or other medications (drug-drug interactions) for which patiromer is more effective or safe?

Conclusions:

- Patiromer was studied in 1 phase 2 trial, a two-part, single blind, phase 3 trial, and a 52-week, open-label randomized, dose-finding phase 2 trial. Major limitations of the data include a high risk of performance bias and selection bias. Generalizability is limited by relatively few study sites within the U.S., significant exclusion criteria, difficult dosing schedules, and a lack of data comparing patiromer to other measures to reduce potassium. In addition, in the primary efficacy study, only patients who initially responded to treatment with patiromer were randomized to the primary trial period, increasing the risk of bias and potentially the beneficial effect of the drug observed. Lastly, this study was sponsored and designed in collaboration by the pharmaceutical company.
- There is low quality evidence that patiromer can decrease serum potassium levels from 0.35 mEq/L to 1.23mEq/L over 4 weeks of therapy in patients with CKD and hyperkalemia on a renin angiotensin aldosterone system (RAAS) inhibitor. The magnitude of potassium decrease is more pronounced with a higher baseline potassium level.
- 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.
- The most common adverse effects seen short-term are gastrointestinal (flatulence, diarrhea, constipation, vomiting, nausea), hypomagnesemia, chronic renal failure, and anemia. There is a boxed warning to administer other oral medications at least 6 hours before or 6 hours after patiromer, due to the potential binding of patiromer to other medications.
- Longer studies are needed to assess the safety of long term use and to appropriately define its place in therapy. It remains unclear, if patiromer will allow for the long term administration of RAAS therapy in patients with CKD or HF and hyperkalemia. Consideration of the risk versus benefit of RAAS inhibitor therapy and adjustment or discontinuation of other medications or herbal treatments that may contribute to serum potassium is necessary.
- Due to the slow onset of patiromer, there is currently no place in the acute treatment of hyperkalemia (≥ 6.5 mEq/L).

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Date: May 2016

Recommendations:

- Defer PDL decisions until a review of sodium polystyrene sulfonate and zirconium cyclosilicate (awaiting FDA approval) at an upcoming P&T meeting.
- Recommend clinical PA criteria to prevent use in the emergent setting or in scenarios not supported by the medical literature (**Appendix 2**).

Background:

Hyperkalemia is common in patients with chronic kidney disease (CKD) or heart failure (HF). Multiple definitions of hyperkalemia exist, including potassium levels over 5.0, 5.5, or 6.0mEq/L.[1] Hyperkalemia is due to altered potassium handling by the kidneys, aldosterone resistance leading to decreased potassium excretion, acidosis or lack of insulin.[2] In HF with reduced ejection fraction, (HFrEF), angiotensin converting enzyme inhibitors (ACEi,), angiotensin II receptor blockers (ARBs), and aldosterone antagonists have been shown to be effective in reducing morbidity and mortality but can also cause hyperkalemia. These medications have also demonstrated the ability to decrease progression of kidney disease in patients with diabetes and CKD. Therefore, the optimization of treatment with these medications is often limited by the development of hyperkalemia.

Hyperkalemia can result in flaccidity of muscles, paralysis, and more seriously can cause life-threatening cardiac arrhythmias and increased mortality.[3] Treatment is indicated in patients with potassium levels over 6mEq/L, or with rapid increases in potassium level.[4, 5] Several medications are used to treat hyperkalemia in the emergent setting (see Table 1). Most of these have a fast onset and work either by shifting potassium intracellularly or by removing potassium from the body. However, there is no data to support the use of these therapies in the setting of chronic hyperkalemia. Although sometimes used chronically in patients, the prolonged use of sodium polystyrene sulfonate (SPS) increases the risk of developing bowel necrosis due to its sorbitol containing formulation. It also has an unpleasant taste, and commonly causes diarrhea. The largest study evaluating SPS involved only 32 patients with either acute or chronic renal disease; however these patients were only treated for up to six days.[6] The only other current option to lower potassium level are loop diuretics. Chronic use of loop diuretics is limited by electrolyte imbalances and they may not be as effective in patients with CKD. Patiromer, a cation exchange polymer, was developed as a potential option for treatment in chronic hyperkalemia. It is not effective for the emergency treatment of life threatening hyperkalemia because of its delayed onset of action.[7] In addition to medications, several other measures may be effective to potentially reduce serum potassium. This includes counselling on a low potassium diet and review of medications that can contribute to an elevated potassium level (NSAID, potassium-sparing diuretic, potassium or herbal supplements). Patiromer is a nonabsorbed polymer that binds potassium in exchange for calcium predominantly in the distal colon, increasing fecal potassium excretion. As it is not absorbed, the amount of calcium absorbed remains small.

Table 1. Acute treatment for hyperkalemia

Shift potassium intracellularly	Remove potassium
Insulin (with glucose)	Diuretics (i.e. loop, thiazide)
Sodium bicarbonate (for metabolic acidosis)	Sodium polystyrene sulfonate
β-2 adrenergic agonists (i.e. albuterol)	

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Black Boxed Warning 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:

Patiromer was studied in 1 phase II trial, a two-part, single blind, phase III trial, and a 52-week, open-label randomized, dose-finding phase II trial for both the prevention and treatment of hyperkalemia. Patients included in the clinical trials had either chronic kidney disease (CKD) or heart failure (HF).

The PEARL-HF trial was a 4 week phase II trial evaluating patiromer for the prevention of hyperkalemia which is an off-label use in patients treated with standard therapy for HF with serum potassium of 4.3 to 5.1 mEq/L. Over half of the patients included had CKD, and 36% had a history of hyperkalemia (7.5% had both CKD and history of hyperkalemia). Overall more normokalemia patients with HFrEF on standard therapy were able to titrate up to spironolactone 50 mg daily and avoid hyperkalemia than patients on placebo.[8] This trial found that the change in potassium with patiromer use was -0.45mEq/L ($p<0.001$). The clinical significance of this difference in potassium is unclear, as even in the placebo group potassium only increased by 0.22 mEq/l. Fewer patients on patiromer experienced hyperkalemia (serum potassium > 5.5 mEq/L) compared to placebo (7.3% vs. 24.5%). Ninety-one percent of patients in the patiromer group and 74% of patients in the placebo group were successfully increased to the higher spironolactone dose ($p=0.019$). However, it is unclear if this increased spironolactone dose has a higher mortality benefit compared to 25 mg, as the mean spironolactone dose achieved in previous HF trials was 26 mg/day.[9] The patients in this study are a good representation of the HF patients who could clinically benefit from patiromer use, as they had other risks for developing hyperkalemia, such as comorbid CKD and more advanced age. However, this study did not evaluate patiromer for the treatment of hyperkalemia in patients with HF.

The primary phase III trial (OPAL-HK) evaluated the use of patiromer in patients with hyperkalemia and CKD receiving RAAS inhibitors (n=243).[12,13] After an initial dose titration period based on baseline potassium level, only patients who responded to therapy were randomized to 8 weeks of either continued patiromer therapy or withdrawal. The primary outcome was reduction in serum potassium after 4 weeks compared to baseline, and compared to placebo in an 8-week withdrawal phase. During the first phase, 62% of patients had moderate-to-severe hyperkalemia and the remainder had mild (38%), and the mean change in serum potassium levels from baseline to week 4 was -1.01 mmol/L (95% CI -1.07 to -0.95) with a larger change in patients with moderate-to-severe hyperkalemia (-1.23 mmol/L) compared to those with mild (-0.65 mmol/L). Only patients whose potassium level had been well-controlled during the initial phase were included in the second phase, increasing the risk of bias and potentially the beneficial effect of the drug observed. After week 8 in the withdrawal phase, fifteen percent of patients in the patiromer group and 60% of patients in the placebo group had hyperkalemia with potassium $\geq$5.5mEq/L, and 43% of the patiromer patients and 91% of the placebo patients had hyperkalemia with potassium $\geq$5.1mEq/L (both $p<0.001$). In an exploratory analysis, 94% of patients in the patiromer group were still receiving RAAS inhibitors at the end of the study. However, risk of bias in this study is high and generalizability is low because the run-in phase resulted in only responders and those with moderate hyperkalemia to be randomized in the 8 week trial. A poorer response is expected in the real world setting. This study was funded by the pharmaceutical company and was designed in colloaboration with the sponsor.

AMETHYST-DN trial was a multicenter, open-label, dose-ranging, phase 2 trial of 324 patients with type 2 diabetes mellitus (T2DM) and CKD.[10,11] This trial consisted of three phases and a post-treatment follow-up phase: during the 4-week run-in, patients with serum potassium less than 5.0 mEq/L were randomized to continue the current ACEi/ARB therapy or switch to losartan 100mg daily. After 2 weeks, if blood pressure was uncontrolled, spironolactone 25mg daily was initiated; this could be increased to 50mg daily for further blood pressure lowering. During the second phase, patients with baseline potassium of 5.0-6.0 mEq/L were included in a third cohort that skipped the run-in phase; this third cohort made up about three-fourths of the study population. Patients from all three cohorts were again randomized to 8 weeks of treatment with patiromer at various doses (4.2-16.8 g BID) based on baseline potassium level. The primary endpoint was the mean central lab serum potassium level from baseline to week 4 of the second phase. Overall, serum potassium level decreased by 0.35-0.97mEq/L, with a higher change in potassium level in the moderate hyperkalemia group. A significant number of patients were not treated per protocol; therefore the effect of patiromer on potassium lowering may be greater than that observed. On the other hand, given the open label design of this study and high non-adherence, there is an increased risk for bias. This could especially have occurred in patients at higher potassium levels, who may have been more careful to avoid other sources of potassium, such as potassium found in the diet. It is therefore difficult to say if patiromer was the sole cause of the larger

potassium change in the moderate hyperkalemia group. The proportion of patients with potassium levels within target range at each scheduled visit of the maintenance phase through week 52 ranged from 83.1% to 92.7% in patients with mild hyperkalemia (n = 180) and from 77.4% to 95.1% in patients with moderate hyperkalemia (n = 66).

There is low quality evidence from these studies to support the use of patiromer to lower potassium levels for duration of 4 weeks. However, the amount of potassium lowering may differ from that seen in the single-blind trials, AMETHYST-DN and OPAL-HK.

Clinical Safety:

The AMETHYST-DN trial demonstrated that the most common adverse reactions (≥1%) of long-term patiromer use include worsening CKD (9.2%) or hypertension (7.9%), hypomagnesemia (8.6%), constipation (6.3%), diarrhea (5.6%), and hypoglycemia (3.3%). The amount of CKD worsening was not defined, although this adverse effect led to 8 patients discontinuing therapy. Although hypomagnesemia was a common adverse reaction, no patients discontinued therapy due to hypomagnesemia, and no patients developed severe hypomagnesemia (<1.0mg/dL). However, this is a potential concern, as low magnesium levels are also associated with ventricular arrhythmias, and may increase the risk of death when in combination with low potassium levels.[8]

See Table 2 for common adverse effects seen with short-term use of patiromer, as seen in the PEARL-HF and OPAL-HK trials. The most common adverse effect found in both studies was gastrointestinal (GI) effects. In general, this was reported to be mild to moderate, with no patients experiencing serious GI effects. In the PEARL-HF trial, magnesium decreased on an average of -0.22mg/dL. However, the incidence of ventricular arrhythmias was no different than placebo. Similarly, magnesium levels decreased by -0.1 to -0.2mg/dL in the OPAL-HK trial; there seemed to be no correlation to magnesium decrease and patiromer dose. Nine patients required magnesium replacement therapy. Although chronic renal failure was reported in the OPAL-HK trial, there was no significant change in renal function reported in either of these trials. Anemia was not discussed.

Another concern is the stated warning/precaution that patiromer binds to many orally administered medications and all medications should be administered 6 hours before or after patiromer due to the risk of decreased absorption. This does not seem to be addressed in any of the patiromer studies. In previous rat studies, patiromer did not affect drug absorption for most drugs that are commonly used in HF and CKD; however bioavailability of valsartan and rosiglitazone was decreased by 30%.[8]

There is low evidence, provided by AMETHYST-DN, that patiromer is safe and effective for use for 52 weeks. Overall, the complications of hyperkalemia (i.e. muscle weakness, arrhythmias) were uncommon; further studies with a larger patient population would be needed to determine if patiromer is able to prevent these complications. Studies did not report any significant difference or any clinically significant changes in ECG parameters, however patients at risk for arrhythmias were excluded from trials.

Table 2. Incidence of common adverse effects with short-term patiromer use

Adverse Effect	**Patiromer (n=666)**	**Placebo**
Constipation	7.2%	0
Hypomagnesemia	5.3%	NA
Diarrhea	4.8%	0
Nausea	2.3%	0
Abdominal discomfort	2.0%	NA
Flatulence	2.0%	NA

Look-alike/Sound-alike Error Risk Potential: None

Pharmacology and Pharmacokinetic Properties:[14]

Parameter	
Mechanism of Action	Increases fecal potassium excretion through binding of potassium in the lumen of the gastrointestinal tract, resulting in a reduction of serum potassium levels.
Absorption	Not systemically absorbed
Distribution and Protein Binding	N/A, not absorbed
Metabolism	N/A, not absorbed
Half-Life	N/A, not absorbed
Elimination	Fecally

Abbreviations: GI=gastrointestinal, N/A=not applicable

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:

1) Long term maintenance of normokalemia
2) Complications of hyperkalemia
3) Discontinuations due to adverse events

Primary Study Endpoint:

1) Mean difference of change in serum K from baseline to 28 days (all three studies)
2) Difference between groups in serum K level after 4 weeks of patiromer discontinuation/continuation

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. Pitt et al. (PEARL-HF)[8] Multicenter, double-blind, RCT, phase 2 study 4 weeks	1. Patiromer 15g BID + spironolactone 2. Placebo + spironolactone	Demographics: Age: 68 years Men: 61% White: 96.5% NYHA II: 55% NYHA III: 42.5% LVEF: 40±12% DM: 32% CKD: 56.5% History of hyperkalemia: 36% CKD and history of hyperkalemia: 7.5% Baseline K: 4.67	ITT: 1. 60 2. 60 mITT: 1. 55 2. 49 PP: 1. 56 2. 49 Attrition: 1. 5 (8.3%)	Primary Endpoint: Mean change in serum K from baseline to 28 days: 1. -0.22mEq/L 2. +0.25mEq/L Difference between groups -0.45mEq/L, p<0.001 Secondary Endpoint: Proportion of patients increased to spironolactone 50mg/d 1. 50/55 (91%)	N/A ARR 48.6% NNT 2	Outcome: GI disorders 1. 21% 2. 6% Discontinuations due to adverse events: 1. 4 (7%) 2. 3 (6%)	5	**Risk of Bias (moderate)**: Selection Bias: method of randomization and allocation concealment is not specified. Patients in the patiromer group had more ACEi/ARB use and ACEi/ARB plus BB use Performance Bias: double-blind design indicated but blinding not described. Detection Bias: double-

		Key Inclusion Criteria: -Age ≥18 years -History of chronic HF with indication to initiate spironolactone -K 4.3-5.1mEq/L -CKD (eGFR <60mL/min) receiving at least 1 HF therapy, or history of hyperkalemia leading to HF therapy discontinuation in the past 6 months Key Exclusion Criteria: -Severe GI disorders -Major GI surgery -Bowel obstruction -Swallowing disorders -Significant primary valvular disease -Known obstructive/restrictive cardiomyopathy -Unstable or stable arrhythmia -recent UA/ACS/TIA -QTc >500ms, BP > 170/90 mm HG, dialysis, elevated LFTs > 3x ULN	2. 11 (18.3%)	2. 36/49 (74%) p=0.019				blind design indicated but blinding not described. No mention was made regarding blinding of the outcome assessors Attrition Bias: Total attrition rate 13% (low), but differential attrition rate 10% Reporting Bias: all endpoints were reported **Applicability**: Patient: Mainly white patients with HF NYHA II and III (97.5%) and CKD (56.5%). Significant exclusion criteria reduce generalizability of results. Intervention: unclear if separated from other medications according Comparator: No data compared to other measures to manage hyperkalemia Outcomes: Primary outcome was a surrogate outcome. Short term study not designed to detect differences in long term complications of hyperkalemia. Setting: Patients were

								enrolled from 38 centers in the US, Germany, Czech Republic, Poland, Ukraine, Russia, and Georgia
2. Weir et al. (OPAL-HK)[12] multinational, single-blind, phase 3 study Phase 1. 4 week single-group, single-blind initial treatment Phase 2. 8 week placebo-controlled, single-blind, randomized withdrawal	**Phase 1** 1. K+ 5.1 - <5.5mmol/L Patiromer 4.2g BID* 2. K+ 5.5 - <6.5 mmol/L Patiromer 8.4g BID* **Phase 2^** 1. Continue patiromer dose from Phase 1* 2. Placebo * titrated to effect based on prespecified algorithm and baseline ^ K+ ≥ 5.5 mmol/L @ baseline AND K+ @ end of phase I was 3.8 to <5.1 mmol /L while on patiromer and RAAS inhibitors.	Demographics: Age: 64 years Men: 58% Stage 3 CKD: 46% Stage 4 CKD: 45% T2DM: 57% HF: 42% HTN: 97% K: 5.6mmol/L Key Inclusion Criteria: -Age 18-80 years -Stage 3-4 CKD (eGFR 15 to <60mL/min) -K 5.1 to <6.5mmol/L (Phase 1) and 5.5 to <6.5 mmol/L (Phase 2) -Stable dose of ≥1 RAAS inhibitor for ≥28 days Key Exclusion Criteria: -K-related ECG changes -Severe GI disorders -Uncontrolled arrhythmias - ventricular arrhythmias -Recent cardiac surgery -Renal/heart	**Phase 1** ITT: 1. 92 2. 151 Completers: 1. 85 (89.5%) 2. 134 (88.7%) **Phase 2** ITT: 1. 55 2. 52 Attrition: 1. 0 (0.0%) 2. 1/52 (1.9%)	**Phase 1** Mean change in serum K level to week 4: both groups -1.01 95% CI -1.07 to -0.95 p<0.001 Proportion of patients with K 3.8 to <5.1mmol/L at week 4: 76% (95% CI 70-81%) **Phase 2** Difference in median change in serum K level: 1. 0.72 mmol/L 2. 0 mmol/L Difference 0.72 mmol/L (95% CI 0.46 to 0.99); p<0.0001 Proportion of patients with recurrent hyperkalemia: 1. 8/55 (15%, 95% CI 6-24%) 2. 31/52 (60%, 95% CI 47-74%) p<0.001	N/A ARR 45.2% NNT 3	Outcome: Supraventricular extrasystoles Patiromer: 2 (4%) Discontinuations due to adverse events: N=10 (group not specified)	34	**Risk of Bias (high)**: Selection Bias: Central randomization occurred, only patients who responded to patiromer were included for randomization Performance Bias: single-blinded design Detection Bias: single-blinded design Attrition Bias: 42.3% of patients in the phase 2 placebo group discontinued prematurely, most commonly due to elevated potassium levels meeting prespecified criteria Reporting Bias: all primary and secondary endpoints were reported **Applicability**: Patient: Poor generalizability due to significant exclusion criteria and the run in phase allowed for only responders and those

		transplant -ACS,TIA/stroke, SBP ≥180/<110 mmHg, DBP ≥110/<60 mmHg -T1DM -HF exacerbation in the past 3 months, NYHA stage IV						with moderate hyperkalemia to be included. Intervention: unclear if separated from other medications according Comparator: No data compared to other measures to manage hyperkalemia Outcomes: Primary outcome was a surrogate outcome. Short term study not designed to detect differences in long term complications of hyperkalemia. Setting: Patients were enrolled from Eastern Europe (24 sites), the European Union (21 sites), and the US (14 sites)
3. Bakris, et al (AMETHYST-DN)[10] Multicenter, open-label, dose-ranging, RCT, phase 2 study	**Treatment phase** *K>5.0-5.5* 1. Patiromer 4.2g BID 2. Patiromer 8.4g BID 3. Patiromer 12.6g BID *K>5.5-6.0* 4. Patiromer 8.4g BID 5. Patiromer	Demographics: Mean Age: 66 years Men: 63.2% White: 100% CKD Stage 3: 64.5% ACEi: 49.3% ARB: 24.3% Mean K: 5.3 Key Inclusion Criteria: -Age 30-80 years -T2DM and CKD (eGFR 15 to <60mL/min), with/out HTN	**Treatment phase** ITT: 1. 74 2. 74 3. 74 4. 26 5. 28 6. 30 PP: 1. 56 2. 51 3. 50	Mean change in central lab serum K level from baseline to week 4 of treatment phase 1. 0.35 (95% CI 0.22-0.48) mEq/L 2. 0.51 (95% CI 0.38-0.63) mEq/L 3. 0.55 (95% CI 0.42-0.68) mEq/L 4. 0.87 (95% CI 0.60-1.14) mEq/L 5. 0.97 (95% CI 0.70-1.23) mEq/L	N/A	Outcome: Worsening CKD: 28 (9.2%) Worsening HTN: 24 (7.9%) Discontinuations due to adverse events: 1. 4 2. 2 3. 7 4. 2	N/A	**Risk of Bias (moderate):** Selection Bias: web-based system used to assign patients to cohorts/starting doses Performance Bias: open-label design Detection Bias: open-label design Attrition Bias: low attrition rate overall (2%), although a significant number of patients were not

	12.6g BID 6. Patiromer 16.8g BID	-Receiving ACEi/ARB/both for ≥28 days prior to screening Key Exclusion Criteria: -Preexisting hyperkalemia with K>5.0, later included pts w/K 5.0 to <6.0 in 3rd cohort	4. 17 5. 21 6. 16 Attrition: 1.1 (1.4%) 2.2 (2.7%) 3.2 (2.7%) 4. 0 5. 1 (3.6%) 6. 0	6. 0.92 (95% CI 0.67-1.17) mEq/L p<0.001 vs. baseline for all changes by hyperkalemia strata and by starting-dose groups within strata Secondary Endpoints: Mean changes in serum K level from baseline to other visits Figure 3		5. 2 6. 2		treated per protocol; the effect of patiromer on K lowering may be greater than observed Reporting Bias: all endpoints were reported **Applicability**: Patient: white patients with CKD (64.5% had stage 3) and T2DM Intervention: unclear if separated from other medications according to package insert. Comparator: Dose-ranging study Outcomes: Primary outcome was a surrogate outcome. Short term study not designed to detect differences in long term complications of hyperkalemia. Setting: Patients were enrolled from 48 sites in 5 European countries.

Abbreviations [alphabetical order]: ACEi = angiotensin converting enzyme inhibitor; ACS = acute coronary syndrome; ARB = angiotensin II receptor blocker; ARR = absolute risk reduction; BB = beta blocker; BID = twice daily; BP = blood pressure; CI = confidence interval; CKD = chronic kidney disease; DBP = diastolic blood pressure; DM = diabetes mellitus; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; GI = gastrointestinal; HF = heart failure; HTN = hypertension; ITT = intention to treat; K = potassium; LVEF = left ventricular ejection fraction; mITT = modified intention to treat; N = number of subjects; N/A = not applicable; NNH = number needed to harm; NNT = number needed to treat; NYHA = New York Heart Association; P4.2 = patiromer 4.2mg twice daily; P8.4 = patiromer 8.4mg twice daily; Pat = patiromer; Pla = placebo; PP = per protocol; QTc = corrected QT interval; RAAS = renin angiotensin aldosterone system; RCT = randomized, controlled trial; SBP = systolic blood pressure; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; TIA = transient ischemic attack; ULN = upper limit of normal; US = United States. GI disorders: flatulence, diarrhea, constipation, vomiting; Recurrent hyperkalemia: one potassium value of 5.5 mmol/L or higher through week 8

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Date: May 2016

Appendix 1: Highlights of Prescribing Information[7]

Black Box Warnings: None

Risk Evaluation Mitigation Strategies: None

Indications: Hyperkalemia
- *Limitations*: Not to be used as an emergency treatment for life-threatening hyperkalemia due to its delayed onset of action

Dosage and Administration: Starting dose 8.4g orally once daily with food
- Adjust dose by 8.4g daily as needed at one-week intervals to obtain desired serum potassium target range
- Doses of patiromer in excess of 50.4g/day have not been tested. Excessive doses of patiromer may result in hyperkalemia. Restore serum potassium if hypokalemia occurs

Formulations: Powder for oral suspension (8.4, 16.8, and 25.2g packets)
- *Active Ingredient*: patiromer sorbitex calcium
- *Inactive Ingredient*: xanthan gum

Contraindications: Known hypersensitivity to patiromer or any of its components

Warnings and Precautions:
- Worsening of gastrointestinal motility; use should be avoided in patients with severe constipation, bowel obstruction or impaction, as patiromer may be ineffective or worsen gastrointenstinal motility.
- Hypomagnesemia,; patiromer binds to magnesium in the colon which could result in hypomagnesmia. This was reported in 5.4% of patients in clinical trials.
- Binding to other oral medications; patiromer binds to many orally administered medications, which could decrease their absorption and reduce their effectiveness. Administer other oral medications at least 6 hours before or 6 hours after patiromer.

Adverse Reactions: Common (incidence $\geq$2%): constipation, hypomagnesemia, diarrhea, nausea, abdominal discomfort, flatulence

Drug Interactions: Take other orally administered drugs at least 6 hours before or after patiromer

Use in Specific Populations:
- *Pregnancy*: patiromer is not absorbed systemically following oral administration and maternal use is not expected to result in fetal risk.
- *Lactation*: patiromer is not absorbed systemically by the mother, so breastfeeding is not expected to result in risk to the infant.
- *Pediatric Use*: safety and efficacy in pediatric patients have not been established

- *Geriatric Use*: of the 666 patients treated with patiromer in clinical studies, 59.8% were age 65 and over, and 19.8% were age 75 and over. No overall differences in effectiveness were observed between these patients and younger patients. Patients age 65 and older reported more gastrointestinal adverse reactions than younger patients.
- *Renal Impairment*: of the 666 patients treated with patiromer in clinical studies, 93% had chronic kidney disease (CKD). No special dosing adjustments are needed for patients with renal impairment.

Storage and Stability: Refrigerate. Must be used within 3 months or being taken out of the refrigerator

Patiromer

Goals:

- Restrict use of patiromer 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.
- Encourage use to optimize medications with demonstrated evidence of mortality reduction in heart failure with reduced ejection fraction.

Length of Authorization:

- 6 to 12 months

Requires PA:

- Patiromer

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 (patient already on patiromer)?	**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. Has the patient tried and failed or cannot tolerate sodium polystyrene?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
5. Does the patient have hyperkalemia requiring emergency intervention (serum potassium ≥6.5 mEq/L)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #6
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, severe constipation)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve up to 6 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 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T Review: *05/16 (EL/MH)*
Implementation: *TBD*