Brand Name: Veltassa

Generic Name: patiromer

Manufacturer[1,2]: Relypsa

Drug Class[1,2]: Potassium binder

Uses:

Labeled Uses[1]: Hyperkalemia in adults and geriatric patients

Unlabeled Uses: None

Mechanism of Action[1,2]:

Patiromer is a cation exchange polymer that contains a calcium-sorbitol counterion. Fecal potassium excretion is increased through binding of potassium in the gastrointestinal lumen, with its principle site of action being the colon. Binding of potassium reduces the concentration of free potassium in the gastrointestinal lumen, resulting in a reduction of serum potassium concentrations.

Pharmacokinetics:

Absorption[1,2,4]: Not systemically absorbed. Serum potassium was reduced significantly by 0.2 mEq/L at 7 hours after the first dose in patients with hyperkalemia and chronic kidney disease who were receiving a controlled-potassium diet (N=25). Patients received patiromer 16.8 g/day as divided doses for 2 days. Serum potassium was reduced by 0.8 mEq/L at 48 hours after the first dose in patients with hyperkalemia and chronic kidney disease who were receiving a controlled-potassium diet (N=25). Patients received patiromer 16.8 g/day as divided doses for 2 days

Metabolism[2,3]:

In radiolabeled ADME studies in rats and dogs, patiromer was not systemically absorbed. Quantitative whole-body autoradiography analysis in rats demonstrated that radioactivity was limited to the gastrointestinal tract, with no detectable level of radioactivity in any other tissues or organs.

Elimination: Excreted in the feces.

Efficacy:

Pitt B, Bakris GL, Bushinsky DA, et al. Effect of patiromer on reducing serum potassium and preventing recurrent hyperkalaemia in patients with heart failure and chronic kidney disease on RAAS inhibitors. Eur J Heart Fail. 2015;17(10):1057-65.

Study Design: 4-week, single-group, single-blind assessment and an 8-week, single-blind, placebo-controlled, parallel group assessment of patiromer withdrawal.

Description of Study: *Methods*: Eligible patients were 18-80 years of age, had stage 3 or 4 CKD [estimated eGFR of 15 mL/min/1.73m^2 to <60 mL/min./1.73 m^2 of body surface area], serum K^+ 5.1 mEq/L to <6.5 mEq/L, indicative of hyperkalaemia, and had been receiving a stable dose of ≥ 1RAASi for ≥ 28 days. This study was carried out in two parts: an initial treatment phase and a randomized withdrawal phase. At the beginning of the initial treatment phase, patients were assigned one of two patiromer doses based on their screening serum K^+ levels. Patients with mild hyperkalemia received 4.2 g of patiromer twice daily; patients with moderate-to-severe hyperkalaemia received 8.4 g of patiromer twice daily. Patiromer was administered as an oral suspension in 40-120 mL of water, depending on dose, with breakfast and dinner. Subsequent doses were adjusted to reach and maintain target serum K^+ levels based on a pre-specified treatment algorithm. Patients who completed the initial treatment phase were eligible to start the randomized withdrawal phase if they had moderate-to-severe hyperkalemia at baseline of the initial treatment phase and were normokalaemic at week 4 of the initial treatment phase. Use of RAASi and recurrence of hyperkalemia were monitored during the randomized withdrawal phase. Hyperkalaemia was defined as a serum K^+ measurement ≥ 5.5 mEq/L during the first 4 weeks of the randomized withdrawal phase, and ≥ 5.1 mEq/L during the last 4 weeks of this phase. Serum K^+ levels were measured at local and central laboratories at baseline, day 3, and weekly throughout both parts of the study. Safety data were recorded at each of these visits. The primary efficacy endpoint of the treatment phase was the mean change in serum K^+ level from baseline to week 4 in patients who received ≥ 1 dose of patiromer and had at least one K^+ after day 3. The secondary endpoint was the proportion of patient whose serum K^+ was within target range (≥3.8 mEq/L to <5.1 mEq/L) at week 4. The primary efficacy endpoint of the randomized withdrawal phase was the difference between patiromer and placebo groups in the median change in serum K^+ from baseline to either week 4 – if serum K^+ stayed in target range— or the earlies visit when serum K^+ was outside that range. *Outcome Results:* A total of 91 (89%) patients with HF completed the initial treatment phase. Of those, 42 patients (465) were not eligible to continue to the randomized withdrawal phase. The mean change in serum K^+ from baseline to week 4 in patients with HF was -1.06 ± 0.05 mEq/L (95% CI -1.16 to -0.95, P< 0.001). The mean change in serum K^+ from baseline to week 4 in HF patients with mild hyperkalaemia (n=38) was -0.74 ± 0.08 mEq/L (95% CI -0.91 to -0.57) for patients with HF with moderate-to severe hyperkalaemia (n=62) the change from baseline was -1.26 ± 0.07 mEq/L (95% CI -1.40 to -1.12). By the end of the 4-week initial treatment phase, 76% of patients with HF achieved a serum K^+ in the target range. The primary and secondary efficacy endpoints were similar in patients without HF. The estimated median change in serum K^+ from baseline to week 4 of the randomized withdrawal phase was 0.74 mEq/L for patients with HF taking placebo and 0.10 mEq/L for those taking patiromer, for a between-group difference of 0.64 mEq/L (95% CI 0.29-0.99; P<0.001). A total of 95% (95% CI 77 to 99) of patients with HF randomized to placebo and

36% (95% CI 19-57) of those randomized to patiromer had at least 1 serum K^+ of ≥ 5.1 mEq/L (P<0.001).

Limitations: This study was supported by Relypsa, Inc., the company that manufactures this medication. Several of the authors received consulting fees from Relypsa, Inc. and one of the authors holds stock from Relypsa, Inc. Results were reported using standard error of the mean as opposed to standard deviation. Standard error is always smaller than the standard deviation, which can be misleading. No placebo or active control was used in the initial treatment phase of this study. This study was not blinded to the investigators. Changed is treatment regimen implemented by the investigator in response to hyperkalaemia or hypokalaemia may have indicated treatment assignment to the patient. No specific instructions for HF diagnosis were provided.

Conclusion: The results of this study showed that patiromer reduced mean serum K^+ to within the normal range in patients with HF. Compared with placebo, patiromer reduced the percentage of patients with recurrent hyperkalaemia. There were no differences in patients with or without HF in regard to these effects of patiromer. This study suggested that patiromer may have an important role in intiating and maintaining RAASI in patients with CKD and HF, with the potential for consequent reduction in cardiovascular death in these high risk patients. More studies should be conducted which involve blinding the investigators with less chance of unblinding to the patient.

Bushinsky, David A et al. "Patiromer Induces Rapid and Sustained Potassium Lowering in Patients with Chronic Kidney Disease and Hyperkalemia." Kidney International 88.6 (2015): 1427–1433. PMC. Web. 16 Mar. 2016.

Study Design: *Methods:* Phase 1, open-lable, single-arm, multi-site study

Description of Study: *Methods:* A total of 29 patients were screened. Twenty-seven patients met the eligibility criteria and were enrolled, entering the potassium- and sodium-restricted diet run-in phase. Eligible patients were admitted to a CRU and began a 3-day controlled metabolic diet (potassium 60 mEq/day and sodium 100 mEq/day) run-in phase. The controlled diet continued throughout the 6-day inpatient stay. Serum potassium was assessed twice daily (i.e., every 10–14 h) during the run-in phase; a separate blood sample was drawn for the assessment of serum potassium at baseline. Assessments of serum potassium were performed by both the local and central laboratory. Local laboratory measurements were used for assessments of study inclusion criteria and for testing related to the clinical care of patients. Central laboratory measurements were used for assessments of baseline values and efficacy and safety. At the end of the run-in, patients with serum potassium 5.5 to <6.5 mEq/l entered the treatment phase and began patiromer 8.4 g twice daily with meals for 2 days, for a total of four doses (i.e., at baseline (time 0) and 10, 24, and 34 h after the first dose). All patients received the same amount of patiromer regardless of their serum potassium. Serum potassium was assessed 1 h before treatment, at baseline just before treatment (time 0), and 4, 7, 10, 12, 14, 17, 20, 24, 28, 31, 34, 36, 38, 41, 44, 48, and 58 h after the first patiromer dose. The primary end point was the change in serum potassium from baseline during the 48 h after the first dose. The time of onset for patiromer was defined as the earliest time point at which the mean change in potassium from baseline was significant <0 mEq/l (P<0.05). The secondary end point was the change in

serum potassium from baseline in prespecified subgroups defined by severity of hyperkalemia at baseline: moderate (serum potassium 5.5–6.0 mEq/l) and severe hyperkalemia (serum potassium >6.0–6.5 mEq/l). *Outcome Results:* after a single dose of patiromer, there was a significant reduction in mean serum potassium by 7 h in moderate-to-severe hyperkalemic CKD patients receiving at least one RAASi while consuming a 60 mEq/day potassium diet. Mean serum potassium continued to decrease and after a second dose of patiromer fell to <5.5 mEq/l by 20 h. By 24 h, more than 80% of patients had a serum potassium ⩽5.5 mEq/l. At 48 h, after four doses of patiromer, mean serum potassium had fallen by 0.75 mEq/l, and more than 90% of patients had serum potassium values ⩽5.5 mEq/l. Over the entire study, mean serum potassium did not increase before the next dose of patiromer. After the last dose of patiromer was administered at 34 h, mean serum potassium was 5.28 mEq/l. Mean serum potassium did not increase for the next 24 h and was 5.27 mEq/l at 58 h. However, mean serum potassium increased significantly at ~86 and 158 h after the last dose of patiromer. No patient developed hypokalemia, and patiromer was well tolerated with only mild adverse events.

Limitations: The authors had full access to the data. Since the authors had full access, they could possibly manipulate the data to suit their needs. The first author wrote the first draft of the introduction and discussion. A medical writer (Wendy Gattis Stough, PharmD), funded by Relypsa, prepared the first draft of the methods and results sections under the supervision of the first author, and Jennifer Tyson (AlphaBioCom), funded by Relypsa, provided additional editorial support. This study was funded by Relypsa, Inc. Dr Bushinsky reports personal fees from Relypsa during the conduct of the study; he reports stock options in Relypsa. Dr Williams reports personal fees from Relypsa; Dr Pitt reports personal fees from Relypsa during the conduct of the study; he reports stock options in Relypsa, Tricida, scPharmaceuticals, DaVinci Therapeutics and Aura Sense. Dr Weir reports personal fees from Relypsa and ZS Pharma, during the conduct of the study. Dr Freeman reports personal fees from Relypsa during the conduct of the study and outside the submitted work, and stock options for involvement in helping design the overall clinical trial program for patiromer. Dr Garza reports employment by Relypsa and stock options in Relypsa during the conduct of the study. Dr Stasiv reports employment by Relypsa and stock options in Relypsa during the conduct of the study. Ms Li reports consulting fees from Relypsa during the conduct of the study. Dr Berman reports employment by Relypsa and stock options in Relypsa, Pfizer and Merck during the conduct of the study. Dr Bakris reports personal fees from Relypsa during the conduct of the study. Standard error of the mean was given, instead of standard deviation, which might have been done because the standard error is always smaller than the standard deviation. No placebo control was used in this study.

Conclusion: In this study, eight adverse events were reported in seven patients. The most common side effects were mild constipation and mild hypotension, each occurring in two patients. There were no side effects that led to a change in study drug dose or its discontinuation, suggesting that these side effects were not serious in nature. Patiromer induced an early and a sustained, clinically significant reduction in serum potassium in moderately and severely hyperkalemic patients with CKD who were taking RAASis. After the first significant decrease in mean serum potassium at 7 h, mean serum potassium levels continued to decrease, never increasing before the next dose or for 24 h after the last dose of patiromer.

Bakris GL, Pitt B, Weir MR, et al. Effect of Patiromer on Serum Potassium Level in Patients With Hyperkalemia and Diabetic Kidney Disease: The AMETHYST-DN Randomized Clinical Trial. JAMA. 2015;314(2):151-61.

Study design: Phase 2, multicenter, open-label, dose-ranging, randomized clinical trial

Description of Study: *Methods:* The open-label study consisted of a screening visit, a run-in period of up to 4 weeks' duration, an 8-week treatment phase followed by a long-term maintenance phase of up to 44 weeks' duration (up to 52 weeks of total treatment), and a posttreatment follow-up period of up to 4 weeks' duration. A total of 306 patients were randomized. Patients with serum potassium levels of 4.3 to 5.0 mEq/L (ie, normokalemic) at the screening visit and who had uncontrolled blood pressure (average sitting systolic blood pressure >130 to ≤180 mm Hg and diastolic blood pressure >80 to ≤110 mm Hg) were entered into the run-in period and randomly assigned in a 3:1 ratio into cohort 1 or cohort 2. A run-in period was conducted to identify patients without hyperkalemia who could potentially benefit from initiation or optimization of RAAS therapy. *Outcome results:* The least squares mean reduction from baseline in serum potassium level at week 4 or time of first dose titration in patients with mild hyperkalemia was 0.35 (95% CI, 0.22-0.48) mEq/L for the 4.2 g twice daily starting-dose group, 0.51 (95% CI, 0.38-0.64) mEq/L for the 8.4 g twice daily starting-dose group, and 0.55 (95% CI, 0.42-0.68) mEq/L for the 12.6 g twice daily starting-dose group. In those with moderate hyperkalemia, the reduction was 0.87 (95% CI, 0.60-1.14) mEq/L for the 8.4 g twice daily starting-dose group, 0.97 (95% CI, 0.70-1.23) mEq/L for the 12.6 g twice daily starting-dose group, and 0.92 (95% CI, 0.67-1.17) mEq/L for the 16.8 g twice daily starting-dose group ($P < .001$ for all changes vs baseline by hyperkalemia starting-dose groups within strata). From week 4 through week 52, statistically significant mean decreases in serum potassium levels were observed at each monthly point in patients with mild and moderate hyperkalemia. Over the 52 weeks, hypomagnesemia (7.2%) was the most common treatment-related adverse event, mild to moderate constipation (6.3%) was the most common gastrointestinal adverse event, and hypokalemia (<3.5 mEq/L) occurred in 5.6% of patients.

Limitations: The study was sponsored and funded by Relypsa. Relpysa and the steering committee designed the study. Relypsa conducted the study, data collection, and management analysis. Relypsa, with the steering committee, was responsible for the interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. Several of the authors received financial compensation from various pharmaceutical companies, including Relypsa.

Conclusions: Among patients with hyperkalemia and diabetic kidney disease, patiromer starting doses of 4.2 to 16.8 g twice daily (8.4-33.6 g/d) resulted in statistically significant decreases in serum potassium levels after 4 weeks of treatment, lasting through 52 weeks.

Contraindications[1,2]:

Hypersensitivity: Patiromer is contraindicated in patients with *a* history of hypersensitivity to patiromer or any of its components.

Precautions[1,2]:

Binding to other oral medications: Administer patiromer 6 hours before or 6 hours after other orally administered medications to prevent patiromer from binding to other oral medications, which may result in decreased gastrointestinal absorption and reduced efficacy of the bound drug. Monitor for clinical response and/or serum concentrations of the other drug, if needed. If adequate dosing separation is not possible between patiromer and the other oral medication, choose to administer patiromer or the other oral medication.

Breast-feeding: According to the manufacturer, patiromer is not absorbed systemically by the mother; breastfeeding is not expected to result in risk to the infant.

Constipation: Avoid use in patients with severe constipation

Fecal impaction: Avoid use in patients with fecal impaction

GI obstruction: Avoid the use in patients with GI obstruction

Hypomagnesemia: Use patiromer cautiously in patients with a history of hypomagnesemia. Patiromer binds to magnesium in the colon. Hypomagnesemia was reported in patients receiving patiromer in clinical trials. Monitor serum magnesium concentrations, and consider magnesium supplementation in patients who develop hypomagnesemia while receiving patiromer.

Pregnancy[1,2,3,4]: Patiromer is not absorbed systemically following oral administration. Although use during pregnancy is not expected to cause risk to the fetus, due to lack of human safety information, patiromer should be used in pregnant women only if clearly needed.

Adverse Effects[2,3]:

Occurring in >1% to <10% of patients

Endocrine/Metabolic

Hypokalemia (4.7%)

Hypomagnesemia (5.3% to 9%)

Gastrointestinal

Abdominal discomfort (2%)

Abnormal gastric motility (no % given)
Constipation (7.2%)
Diarrhea (4.8%)
Flatulence (2%)
Nausea (2.3%)

Occurring in <1% of patients

Immunologic Effects

Hypersensitivity reaction (0.3%)

Drug Interactions[1,2]:

Administer other oral medications at least 6 hours before or after patiromer. During in vitro binding studies, patiromer was shown to bind about half of the oral medications tested. Binding of patiromer to other orally administered medications may result in decreased gastrointestinal absorption and reduced efficacy of the bound drug. Monitor for clinical response and/or blood concentrations of the other drug, if needed. If adequate dosing separation is not possible between patiromer and the other oral medication, choose to administer patiromer or the other oral medication.

Dosing/Administration[1,2,3,4]:

Adult Dosing

Initial dose: 8.4 g PO once daily. Monitor serum potassium, and adjust dose by 8.4 g daily as needed at 1 week or longer intervals to obtain the desired serum potassium target range, up to a maximum dose of 25.2 g once daily.

Adolescents, children, infants, neonates

Safety and efficacy have not been established

Hepatic impairment

Specific guidelines for dosage adjustments in hepatic impairment are not available; it appears that no dosage adjustments are needed.

Renal impairment

Specific guidelines for dosage adjustments in renal impairment are not available; it appears that no dosage adjustments are needed.

Conclusion:

Patiromer appears to be an effective therapy for hyperkalemia in patients with renal impairment, which was a co-morbidity present in all of the patients in these studies. Patiromer should not be used for immediate correction of hyperkalemia because of its delayed onset of action. Other oral medications should be separated by 6 hours (either before or after dosing patiromer) because of the fact that patiromer has the ability to bind many orally administered medications. The amount of adverse effects associated with patiromer appears to be few in number and relatively mild. Although specific drug interactions were not provided, in vitro studies have shown that there are a significant number of medications that can be bound by patiromer. Further studies should be conducted with long-term (< 1 year) patiromer to see if any additional safety or efficacy data can be provided.

Recommended References:

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7. Bakris GL, Pitt B, Weir MR, et al. Effect of Patiromer on Serum Potassium Level in Patients With Hyperkalemia and Diabetic Kidney Disease: The AMETHYST-DN Randomized Clinical Trial. JAMA. 2015;314(2):151-61.