CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Patiromer (Veltassa)

Indication: Treatment of hyperkalemia in adults with chronic kidney disease

Recommendation: Reimburse with Conditions

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Single Technology

PATIROMER (VELTASSA — OTSUKA CANADA PHARMACEUTICAL INC.)

Therapeutic Area: Hyperkalemia, adults (chronic kidney disease)

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that patiromer should be reimbursed for the treatment of hyperkalemia in adults with chronic kidney disease only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Patiromer was efficacious in reducing serum potassium levels and maintaining normal serum potassium levels in one two-part study (OPAL-HK). Patients enrolled in the study had hyperkalemia (baseline serum potassium of 5.1 to < 6.5 mmol/L) and chronic kidney disease (baseline estimate glomerular filtration rate [eGFR] of 15 to < 60 mL/min/1.73 m^2) who were receiving a stable dose of at least one renin-angiotensin-aldosterone system inhibitor (RAASi). Patiromer statistically significantly reduced serum potassium levels by -1.01 mmol/L (95% confidence interval [CI], -1.07 to -0.95; P < 0.001) from baseline to week four in part A of the study. The percentage of patients with a serum potassium level within the target range (3.8 to < 5.1 mmol/L) was 76% (95% CI, 70% to 81%) at week four in part A. In patients who continued to part B of OPAL-HK, treatment with patiromer for four weeks caused no change in serum potassium (median 0 mmol/L), whereas there was an increase of a median of 0.72 mmol/L in the group that received placebo (P < 0.001). An exploratory analysis indicated that 73% of patients treated with patiromer in part B did not require additional modification of RAASi or patiromer doses for recurrent hyperkalemia compared with 33% of patients in the placebo group. Patients expressed a desire for more palatable therapies to control hyperkalemia without highly restrictive diets.

The submitted price of patiromer is $9.80 per sachet, with an estimated annual cost ranging from $3,577 to $7,154 per patient depending on the strength used. CADTH re-analyses of the pharmacoeconomic model estimated the incremental cost-effectiveness ratio (ICER) of patiromer plus current practice compared with current practice alone to be $475,196 per quality-adjusted life-year (QALY). A price reduction is required for the ICER to be below a $50,000 per QALY willingness to pay (WTP) threshold.

Table 1. Reimbursement Conditions and Reasons

Reimbursement Condition	Reason
Initiation	
1. Patient has hyperkalemia in the setting of chronic kidney disease with a confirmed eGFR of >15 mL/min/1.73 m^2 and < 60 mL/min/1.73m^2	Population enrolled in the OPAL-HK study.
2. Patient is receiving RAASi therapy	Population enrolled in the OPAL-HK study.
Discontinuation	
1. Patient is no longer receiving RAASi therapy	Permitting patients to remain on a therapeutic dose of RAASi is a key clinical outcome. If a patient is no longer on RAASi then patiromer should be discontinued.
2. Patient requires dialysis (eGFR < 15 ml/min/1.73m^2)	The Health Canada indication is for patients with an eGFR of 15 ml/min/1.73m^2 or greater. Patients in OPAL-HK were discontinued from patiromer if they required dialysis.
Prescribing	
Patients should not be receiving another potassium binder concurrently with patiromer.	There is no evidence for efficacy or safety of combining patiromer with other potassium binding medications
Pricing	
A reduction in price	CADTH reanalysis indicated an ICER of $475,196/QALY, and therefore an 85% price reduction would be needed to meet a $50,000/QALY WTP threshold. The ICER would increase, requiring a greater price reduction for patiromer to be considered cost effective, if: it is used long term; more patients use the maximum dose; and/or the benefit on RAASi administration is lower.

eGFR = estimated glomerular filtration rate; iCER = incremental cost utility ratio; QALY = quality-adjusted life-year; RAASi = renin-angiotensin-aldosterone system inhibitor; WTP = willingness-to-pay

Implementation Guidance

RAASi treatment would include the following: angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), and mineralocorticoid receptor antagonists (MRAs).

Discussion Points

- OPAL-HK included patients with serum potassium levels from 5.1 mmol/L to < 5.6 mmol/L. CDEC heard clinician expert input that patients with initial potassium levels in this range would typically not be treated with a pharmacological agent for hyperkalemia. Therefore, the generalizability of the overall study results to clinical care is unclear. Moreover, there is no evidence that patiromer improves patient relevant outcomes, such as survival, cardiovascular and renal outcomes, prevents hospitalization or emergency department visits, or improves health-related quality of life.

- A longer-term phase II study, AMETHYST-DN (N = 304), demonstrated patiromer maintained serum potassium in the target range of 3.8 to < 5.1 mmol/L in approximately 80% of patients during the 44-week maintenance period. However, there is no longer-term data for the effects of patiromer on clinical outcomes.

- The absence of comparative data was considered a key limitation of the evidence base for patiromer.
- Given the expected place in therapy in patients requiring continued RAASi therapy, CDEC determined it was likely that patiromer would be used in the long term and therefore did not agree with the sponsor's assumption that most patients would discontinue by one year. Relaxation of this assumption in re-analyses caused the ICER to increase. CDEC concluded that, based on these results, the 85% price reduction needed to achieve a $50,000 per QALY ICER is likely conservative.
- Patients expressed a desire for more palatable therapies for controlling hyperkalemia, but CDEC noted that these outcomes were not studied in OPAL-HK.

Background

Patiromer has a Health Canada indication for the treatment of hyperkalemia in adults with chronic kidney disease (eGFR ≥15mL/min/1.73m^2). It is a potassium binding cation exchange polymer that uses a calcium-sorbitol complex as a counterion. Patiromer binds to potassium in the gastrointestinal tract and increases fecal potassium excretion. Patiromer is available as individual sachets containing 8.4 g, 16.8 g, or 25.2 g of patiromer sorbitex calcium powder for oral suspension, although only the 8.4 g or 16.8 g sachets are marketed. The Health Canada recommended starting dose of patiromer is 8.4 g once daily. The daily dose may be adjusted by 8.4 g at intervals of one week or longer based on serum potassium level and the desired target range, up to a maximum of 25.2 g per day. The product monograph notes that, given the delayed onset of action (4 to 7 hours after administration), patiromer should not be used for emergency treatment for life-threatening hyperkalemia.

Summary of Evidence

To make their recommendation, the Committee considered the following information:

- A review of one single-blind, phase III clinical study in patients with hyperkalemia and chronic kidney disease.
- Patients' perspectives gathered by one patient group, the Kidney Foundation of Canada.
- Input from one clinical specialist with expertise diagnosing and treating patients with hyperkalemia and kidney disease.
- Input from two clinician groups, one from an individual clinician at Sunnybrook Hospital and one input on behalf of 10 clinicians at the Scarborough Regional Nephrology Program.
- A review of the pharmacoeconomic model and report submitted by the sponsor

Summary of Patient Input

One patient group, the Kidney Foundation of Canada, provided input for this submission. Patient perspectives were obtained from a survey. The following is a summary of key input from the perspective of the patient group. Notably, respondents focused on the disease burden and treatment regimen for chronic kidney disease:

- Chronic kidney disease negatively impacts the physical and/or mental health and the daily routine, especially one's career, of patients and caregivers.
- Patients indicated that early stages of chronic kidney disease can be managed with medication, lifestyle changes, and reducing dietary sodium and potassium intake. A number of patients had experience with SPS, CPS, and patiromer treatment; these respondents indicated dissatisfaction with the texture, frequency of administration, and taste of SPS and CPS. In advanced stage such as kidney failure, dialysis and kidney transplant become the only option, which heavily restricts day-to-day life, and requires patients to limit potassium intake through highly restrictive diets to avoid hyperkalemia between treatments.
- Survey respondents expected new therapies to be affordable, effective, associated with minimal adverse effects, have convenient administration (e.g., frequency and ease), facilitate life with chronic kidney disease with ease, and help improve quality of life.

Clinical Trials

The CADTH systematic review included one single-blind (patient blinded), phase III trial of patients with hyperkalemia (serum potassium levels from 5.1 mmol/L to < 6.5 mmol/L) and chronic kidney disease (eGFR from 15 to < 60 mL/min/1.73 m^2) who were receiving a stable dose of at least one RAASi. The study had two sequential parts. The first part (part A) was a 4-week non-randomized treatment phase, during which 92 and 151 patients received 8.4 g/day or 16.8 g/day of patiromer if their screening serum potassium was 5.1 to < 5.5 mmol/L or 5.5 to < 6.5 mmol/L, respectively. The second part (part B) was an 8-week, randomized, withdrawal phase, during which responders to patiromer treatment in part A (achieved serum potassium within 3.8 and < 5.1 mmol/L, who had a baseline serum potassium of ≥ 5.5 mmol/L [maximum <6.5 mmol/L]) received 8g per day placebo (n = 52) or patiromer (n = 55) at their regular dose.

An important limitation of the trial is the selective patient population in each part that limits the generalizability of the results. Patients included in part A of the trial had no significant comorbidities and most had mild hyperkalemia (< 6.0 mmol/L). Part B of the trial only included those who responded to patiromer and some were randomized to withdrawal of treatment (placebo). This enrichment design may augment the treatment benefits, minimize side effects, and result in high adherence, something that may not occur to the same extent in the patient population in clinical settings. As well, clinical outcomes that are relevant to patients, such as survival, cardiovascular and renal outcomes, hospitalization or emergency department visits, and health-related quality of life were not evaluated.

Outcomes

Outcomes were defined a priori in CADTH's systematic review protocol. Of these, CDEC discussed the following: change from baseline in serum potassium, proportion of patients with a serum potassium within normal range (3.8 to < 5.1 mmol/L) and higher than normal (≥ 5.5 mmol/L), and proportion of patients requiring adjustments to concomitant RAASi dosing.

The primary outcome in OPAL-HK was the change in serum potassium from the respective baseline to Week 4 of each part of the study.

Efficacy

In part A of OPAL-HK, the mean (standard error [SE]) changes from baseline in serum potassium at Week 4 were -0.65 (0.049) mmol/L and -1.23 (0.04) mmol/L in patients with baseline serum potassium levels of 5.1 to < 5.5 mmol/L or 5.5 to < 6.5 mmol/L, respectively. With the two groups combined, there was a statistically significant mean change of -1.01 mmol/L in serum potassium from baseline through Week 4 (95% CI, -1.07 to -0.95 mmol/L; P < 0.001). The threshold value for serum potassium change from baseline set by the FDA to be considered clinically important is 0.7 mmol/L or greater. The percentage of patients with a serum potassium level within the target range (≥ 3.8 to < 5.1 mmol/L) at Week 4 was 76% (95% CI, 70% to 81%) in the total population (both dose groups), with similar percentages in each dose group (74% and 77% in dose group 1 and 2, respectively).

For the group of patients who were responders to treatment and continued into part B, patients randomized to placebo group had a median increase of 0.72 mmol/L in serum potassium from a baseline of 4.45 mmol/L, whereas the patiromer group had 0.00 median change from a baseline level of 4.49 mmol/L. The estimated between-group difference in median change was statistically significant (0.72 mmol/L, P < 0.001).

A statistically significantly greater percentage of patients in the placebo group of part B had a serum potassium level outside of the target range (≥ 5.1 and ≥ 5.5 mmol/L) compared to patiromer: 91% versus 43% for ≥ 5.1 mmol/L and 60% versus 15% for ≥ 5.5 mmol/L, respectively (P < 0.001 for both).

The percentage of patients requiring concomitant RAASi dosing and patiromer dose adjustments through to week weight was an exploratory analysis in part B. Overall, 73% of patients on patiromer did not require additional modification of RAASi or patiromer doses for recurrent hyperkalemia to complete the second part of the trial, compared to 33% of patients on placebo. In the placebo group, 66% and 56% of patients had a reduction of RAASi dose or complete discontinuation of RAASi because of hyperkalemia, respectively. In contrast, 6% of patients in the patiromer group had a reduction and discontinuation of RAASi because of

hyperkalemia each. By the end of the trial, more patiromer-treated patients (94%) were still receiving RAASi medication than placebo patients (44%).

Harms (Safety)

In the first part of the trial, a similar percentage of patients (46% and 48% in the two dose groups) experienced adverse events. The most commonly reported adverse events included gastrointestinal disorders, with constipation reported for more than 5% of patients in both groups. During part B, 50% and 47% of patients in the placebo and patiromer groups, respectively, experienced adverse events.

A total of four patients had serious adverse events throughout the study and 17 patients withdrew from the study due to adverse events. One person died due to mesenteric vessel thrombosis that was considered to be unrelated to treatment by the investigators.

Among notable harms, constipation was reported for 11% and 4% patients in the first and second part of the trial, respectively, while diarrhea, hypomagnesemia, and hypokalemia was reported by <5% of patients in either part, regardless of treatment. Due to the short duration of the trial (12 weeks), important safety signals may not have been captured. Health Canada's assessment of pooled data, including data from four phase II and III trials, with duration ranging from 28 days to one year, did not identify new or major safety signals, such as intestinal perforation or necrosis. Nonetheless, there remains a need for longer-term safety data for patiromer.

Indirect Evidence

No indirect treatment comparisons were not submitted by the sponsor, nor were any identified from the literature.

Other Relevant Evidence

AMETHYST-DN was an open-label, dose ranging, phase II trial with one year of follow-up data that provided supportive evidence of the longer-term efficacy and safety of patiromer treatment. Enrolled patients (N = 304) had hypertension and diabetic nephropathy receiving ACEis and/or ARBs, with or without spironolactone. A total of 266 patients completed the 8-week initiation period and 197 patients completed the entire study period.

The primary endpoint (central laboratory values) was achieved: the mean change from baseline in serum potassium at week 4 (or prior to dose titration) was statistically significant for all starting dose groups within both baseline serum potassium strata ($P < 0.001$). The least square mean changes in serum potassium at week 4 was overall -0.47 mmol/L in stratum 1 (> 5.0 to 5.5 mmol/L) and -0.92 mmol/L in stratum 2 (> 5.5 to < 6.0 mmol/L). Most patients (97.7%) reached the target potassium range (3.8 to 5.0 mmol/L) during the 8-week treatment initiation period and maintained target levels (mean ranging from 4.5 to 4.8 mmol/L) during the long-term maintenance period. Serum potassium was within the target range for approximately 80% maintenance period.

Greater than two-thirds (65.8%) of patients in stratum 1 and 77.4% of patients in stratum 2 experienced an adverse event, with gastrointestinal events occurring most frequently. Two patients in each stratum experienced gastrointestinal perforation, ulceration, hemorrhage, or obstruction. A total of 15 deaths occurred, 9 (4.1%) in stratum 1 and 6 (7.1%) in stratum 2; none were considered related to patiromer. Other serious adverse events were reported in 13.2% and 17.9% of patients in strata 1 and 2, respectively.

Cost and Cost-Effectiveness

The submitted cost of patiromer is $9.80 per sachet regardless of strength. At a daily dose of 8.4 to 16.8 g, the annual cost is $3,577 per patient. At a maximum daily dose of 25.2 g, the annual cost is $7,154 per patient.

The sponsor submitted a Markov model to predict outcomes associated with hyperkalemia and to capture costs and effects associated with patiromer plus current practice compared to current practice alone. The model consisted of 26 health states. Each chronic kidney disease stage (3 or 4) was split into nine health states related to the patient's serum potassium level (<5.5, 5.5-6.0, and >6.0 mmol/L) and whether they had experienced a cardiac event (no event, cardiac event, post cardiac event). If the patient's serum potassium level was less than 5.5 mmol/L, then it was assumed they would receive a full RAASi dose. If the patient's serum potassium level was 5.5 to 6.0 mmol/L, then they would receive a reduced dose (50% of full dose). If the patient's serum potassium

level rose above 6.0 mmol/L, then they would discontinue their RAASi, Patients could also progress sequentially through chronic kidney disease stages to end stage kidney disease and could experience death from any of the health states. Patents could experience a cardiac event and either die or move to the post-cardiac event stage at any point. The OPAL-HK trial was used to inform the likelihood of a patient's serum potassium level changing. Probabilities related to all other events were sourced from the literature. The time horizon in the base case was 35 years to capture the maximum lifetime of a patients with a modelled starting age of 65, with a 1.5% annual discount rate for costs and effects and a monthly cycle length.

CADTH identified the following key limitations with the sponsor's pharmacoeconomic analysis:

- The sponsor assumed increased all cause acute hospitalization for six months for patients experiencing hyperkalemia based on a Danish observational study. Hospitalization due to hyperkalemia was not measured within the trial, nor was the assumption that treatment with patiromer would reduce acute all cause hospitalization over a subsequent six-month period.
- The OPAL-HK trial was 12 weeks long, with serum potassium measured as a surrogate outcome. All health benefits in the economic model are mediated through the benefits of RAASi use, with the assumption that management of hyperkalemia will result in greater RAASi use, which in turn would improve health. There is significant uncertainty regarding the relationship between serum potassium levels and RAASi use and likewise the health consequences of increased RAASi use. Neither of these outcomes was explored in the clinical trial.
- The sponsor assumed a daily use of one sachet (8.4g or 16.8g per day, flat priced). However, OPAL-HK reported a mean daily dose of 21 g, indicating a significant proportion would be on a dose greater than 16.8 g per day with twice the daily cost.
- Discontinuation was estimated from an exponential curve based on OPAL-HK data over eight weeks for patriromer. In the clinical trial actual use was 81% after eight weeks but modeled to be 30% at one year and no use at 4.5 years. According to the CADTH clinical expert, in those patients that initially tolerate patiromer, it is likely to be used long-term if approved.

CADTH undertook reanalyses to address the identified limitations: removing the acute hospitalization benefit associated with patiromer; increasing the treatment dose to align with the trial; and, using RAASi benefits as reported in the literature. CADTH could not address several limitations with the sponsor's submission such as the uncertainty associated with the long term comparative clinical effects of patiromer and the potential for long term treatment use. Based on CADTH re-analyses, patiromer is not cost effective at a $50,000 WTP threshold at an ICER $$475,196 per QALY gained compared to current practice. A price reduction of 85% would be required for patiromer to be considered optimal at a WTP threshold of $50,000 per QALY. CADTH scenario analyses that varied the benefits associated with RAASi use (changing the NMA OR inputs by 20%) resulted in changes to the CADTH base case to range from $287,671 to over $1 million per QALY. Assuming long term treatment use increased the ICER to over $4 million per QALY. Given this uncertainty, the CADTH base case ICER may be underestimated.

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Sally Bean, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Allen Lefebvre, Dr. Kerry Mansell, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

April 21, 2021 Meeting

Regrets

Three expert committee members did not attend.

Conflicts of Interest

None

CADTH

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