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CADTH Reimbursement Recommendation

Patiromer (Veltassa)

Indication: Treatment of hyperkalemia in adults with chronic kidney disease

Sponsor: Otsuka Canada Pharmaceutical Inc.

Final Recommendation: Reimburse with conditions

CADTH

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Redactions: Confidential information in this document has been redacted at the request of the sponsor in accordance with the *CADTH Drug Reimbursement Review Confidentiality Guidelines.*

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Summary

What is the CADTH reimbursement recommendation for Veltassa?

CADTH recommends that Veltassa should be reimbursed by public drug plans for the treatment of hyperkalemia if certain conditions are met.

What are the conditions for reimbursement?

Veltassa should only be reimbursed if the cost is reduced.

Which patients are eligible for coverage?

Veltassa should only be covered to treat adult patients with chronic kidney disease who have hyperkalemia and who are receiving renin-angiotensin-aldosterone system inhibitor therapy.

Why did CADTH make this recommendation?

Evidence from a clinical trial demonstrated that Veltassa was effective at achieving and maintaining normal potassium levels in patients with hyperkalemia and chronic kidney disease. Veltassa also appeared to allow patients to continue treatment with their renin-angiotensin-aldosterone system inhibitor. Based on public list prices, Veltassa is not considered cost-effective at a willingness to pay of $50,000 per quality-adjusted life-year for the indicated population relative to standard of care. A price reduction is therefore required.

Key Messages

- Clinical evidence suggests that Veltassa should be reimbursed to treat hyperkalemia in adult patients with chronic kidney disease and who are receiving renin-angiotensin-aldosterone system inhibitor therapy.
- Economic evidence suggests that at least an 85% price reduction is needed to ensure Veltassa is cost-effective at a $50,000 per quality-adjusted life-year threshold.
- Higher price reductions may be required if Veltassa is used long term, more patients use the maximum dose, and/or the benefit of renin-angiotensin-aldosterone system inhibitor administration is lower.
- Based on public list prices, the 3-year budget impact is $86,948,298.

What is hyperkalemia?

Hyperkalemia is when the potassium level in the blood is higher than normal (greater than 5.0 mmol/L). Potassium is an essential element for the function of muscles and nerves. Hyperkalemia is mainly caused by increased potassium release from cells and reduced potassium elimination in urine, both of which may result from various clinical conditions (most commonly kidney failure) or from medications (e.g., drugs that inhibit the renin-angiotensin-aldosterone system). The exact frequency of hyperkalemia in the general population is unknown but has been estimated to be associated with 2.6% of emergency room visits and 3.5% of hospital admissions in Canada.

What is Veltassa?

Veltassa is approved by Health Canada for the treatment of hyperkalemia in adults with chronic kidney disease. It is a medication taken by mouth. Veltassa works by binding potassium from ingested food in the intestine and preventing it from being absorbed into the body. Restricting dietary uptake in this way leads to decreases in potassium levels in the blood.

How much does Veltassa cost?

Treatment with Veltassa is expected to cost approximately $3,577 to $7,154 per patient annually depending on dose.

What other treatments are available for hyperkalemia?

There are other treatments available for hyperkalemia, including limiting dietary intake of potassium-rich foods, stopping or reducing the dose of medications that increase blood potassium, diuretics, laxatives, oral bicarbonate, and potassium binders (cation-exchange resins).

Unmet needs in hyperkalemia

Patients expressed a need for more palatable oral medications that lower potassium in the blood while they continue to take the therapies that are protective for their kidneys and heart (e.g., renin-angiotensin-aldosterone system inhibitors).

How much do other treatments cost?

Cation-exchange resins cost between $507 to $8,464; however, these are infrequently used. Therefore, Veltassa would be an add-on therapy for most patients.

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 2-part study (OPAL-HK). Patients enrolled in the study had hyperkalemia (baseline serum potassium of 5.1 mmol/L to < 6.5 mmol/L) and chronic kidney disease (baseline estimate glomerular filtration rate [eGFR] of 15 mL/min/1.73 m^2 to < 60 mL/min/1.73 m^2) who were receiving a stable dose of at least 1 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 mmol/L; P < 0.001) from baseline to week 4 in part A of the study. The percentage of patients with a serum potassium level within the target range (3.8 mmol/L to < 5.1 mmol/L) was 76% (95% CI, 70% to 81%) at week 4 in part A. In patients who continued to part B of OPAL-HK, treatment with patiromer for 4 weeks caused no change in serum potassium (median = 0 mmol/L), whereas there was an increased 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 reanalyses 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 less than a $50,000 per QALY willingness-to-pay (WTP) threshold.

Implementation Guidance

1. RAASi treatment would include the following: angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists.
2. The product monograph for patiromer notes that, given the delayed onset of action (4 to 7 hours after administration), patiromer should not be used for emergency treatment of life-threatening hyperkalemia. Patients enrolled in the OPAL-HK study had serum potassium levels from 5.1 mmol/L to less than 6.5 mmol/L. Patients were excluded from the study if they had hyperkalemia requiring emergency intervention or potassium-related ECG changes.

Discussion Points

- Among the patients enrolled into OPAL-HK were those with serum potassium levels from 5.1 mmol/L to less than 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 mmol/L to less than 5.1 mmol/L in approximately 80% of patients during the 44-week maintenance period. However, there are 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.

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/1.73 m^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/1.73 m^2)	The Health Canada indication is for patients with an eGFR of ≥ 15 mL/min/1.73 m^2. 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 per QALY; therefore, an 85% price reduction would be needed to meet a $50,000 per 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.

- Given the expected place in therapy for 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 1 year. Relaxation of this assumption in the reanalyses 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/1.73 m^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 and 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 1 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 of life-threatening hyperkalemia.

Summary of Evidence

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

- A review of 1 single-blind, phase III clinical study in patients with hyperkalemia and chronic kidney disease
- Patients' perspectives gathered by 1 patient group, the Kidney Foundation of Canada
- Input from 1 clinical specialist with expertise diagnosing and treating patients with hyperkalemia and kidney disease
- Input from 2 clinician groups: 1 an individual clinician at Sunnybrook Hospital and 1 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 daily routine, especially the 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 sodium polystyrene sulphonate (SPS), calcium polystyrene sulphonate (CPS), and patiromer treatment; these respondents indicated dissatisfaction with the texture, frequency of administration, and taste of SPS and CPS. In advanced stages, such as kidney failure, dialysis and kidney transplant become the only options, 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 1 single-blinded (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 mL/min/1.73 m^2 to < 60 mL/min/1.73 m^2) who were receiving a stable dose of at least 1 RAASi. The study had 2 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 mmol/L to < 5.5 mmol/L or 5.5 mmol/L 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 mmol/L and < 5.1 mmol/L, who had a baseline serum potassium of ≥ 5.5 mmol/L [maximum <6.5 mmol/L]) received 8 g per day of placebo (n = 52) or patiromer (n = 55) as their regular dose.

An important limitation of the trial was the selective patient population in each part, which 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 mmol/L 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 mmol/L to less than 5.5 mmol/L or 5.5 mmol/L to less than 6.5 mmol/L, respectively. With the 2 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 mmol/L 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 groups 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 mmol/L and ≥ 5.5 mmol/L) compared with patiromer: 91% versus 43% for ≥ 5.1 mmol/L and 60% versus 15% for ≥ 5.5 mmol/L, respectively (P < 0.001 for both).

An exploratory analysis in part B was the percentage of patients requiring concomitant RAASi dosing and patiromer dose adjustments through to week 8. 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 with 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. 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 2 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 4 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 were reported by less than 5% of patients in both parts, 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 4 phase II and III trials with durations ranging from 28 days to 1 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 identified in the literature.

Other Relevant Evidence

AMETHYST-DN was an open-label, dose-ranging, phase II trial with 1 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 and were receiving ACE inhibitors and/or angiotensin receptor blockers, 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 end point (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 were–0.47 mmol/L in stratum 1 (> 5.0 mmol/L to 5.5 mmol/L) overall and –0.92 mmol/L (> 5.5 mmol/L to < 6.0 mmol/L).in stratum 2. Most patients (97.7%) reached the target potassium range (3.8 mmol/L to 5.0 mmol/L) during the 8-week treatment initiation period and maintained target levels (means ranging from 4.5 mmol/L to 4.8 mmol/L) during the long-term maintenance period. Serum potassium was within the target range for approximately 80% maintenance period.

More 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 g 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 with current practice alone. The model consisted of 26 health states. Each chronic kidney disease stage (3 or 4) was split into 9 health states related to the patient's serum potassium level (< 5.5 mmol/L, 5.5 mmol/L to 6.0 mmol/L, 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 mmol/L 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 patient with a modelled starting age of 65 years and 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 6 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 6-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 were mediated through the benefits of RAASi use, with the assumption that management of hyperkalemia would 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 1 sachet (8.4 g or 16.8 g 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 of patiromer was estimated from an exponential curve based on OPAL-HK data over 8 weeks. In the clinical trial, actual use was 81% after 8 weeks but modelled to be 30% at 1 year and no use at 4.5 years. According to the CADTH clinical expert, in those patients who 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 reanalyses, patiromer is not cost-effective at a $50,000 WTP threshold at an ICER of $475,196 per QALY gained compared with 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 more than $1 million per QALY. Assuming long-term treatment use increased the ICER to more than $4 million per QALY. Given this uncertainty, the CADTH base-case ICER may be underestimated.

Members of the Canadian Drug Expert Committee

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.

Meeting date: April 21, 2021

Regrets: Three expert committee members did not attend.

Conflicts of interest: None