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CADTH COMMON DRUG REVIEW

# CADTH Canadian Drug Expert Committee Recommendation

(Final)

**SODIUM ZIRCONIUM CYCLOSILICATE (LOKELMA — ASTRAZENECA CANADA INC.)**
Indication: Hyperkalemia.

**RECOMMENDATION**
The CADTH Canadian Drug Expert Committee recommends that sodium zirconium cyclosilicate should not be reimbursed for the treatment of hyperkalemia in adults.


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# SODIUM ZIRCONIUM CYCLOSILICATE (LOKELMA — ASTRAZENECA CANADA INC.)

Indication: Hyperkalemia.

## Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that sodium zirconium cyclosilicate should not be reimbursed for the treatment of hyperkalemia in adults.

## Reasons for the Recommendation

1. There is insufficient evidence that sodium zirconium cyclosilicate addresses any of the clinical needs of patients with hyperkalemia that are not already met by other treatments that are currently reimbursed. Data from several randomized controlled trials (RCTs) indicated that sodium zirconium cyclosilicate is more effective than placebo in reducing elevated serum potassium levels and maintaining normokalemia. However, the lack of comparative evidence precludes any conclusions be made regarding the comparative effectiveness of sodium zirconium cyclosilicate on achieving and maintaining normal serum potassium levels, or on outcomes such as survival, cardiovascular and renal outcomes, health-related quality of life, and adverse effects. Therefore, it is unclear whether sodium zirconium cyclosilicate provides similar or additional clinical value compared with other medications currently reimbursed for managing hyperkalemia.
2. Limitations in the evidence prevented CDEC from identifying subpopulations in whom sodium zirconium cyclosilicate may provide additional benefit for patients and/or be relatively cost-effective. This included the sponsor-requested reimbursement maintenance therapy population of patients with chronic kidney disease with an estimated glomerular filtration rate (eGFR) of less than 30 mL/min/1.73 $m^2$ who have experienced at least two hyperkalemic events and are suboptimally managed on renin angiotensin aldosterone system inhibitor (RAASi) therapy. However, none of the RCTs evaluated the effects of sodium zirconium cyclosilicate in this specific subpopulation and CDEC was unable to identify any other subpopulations.

## Discussion Points

- Although the clinical trials demonstrated that sodium zirconium cyclosilicate lowers serum potassium in correction and outpatient maintenance settings, the clinical relevance of these findings is uncertain. The trials with correction phases included a variable proportion of patients with blood potassium levels from 5.0 mmol/L to 5.5 mmol/L (up to 60% of patients randomized in the pivotal Study ZS-003). 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 applicability of the study results — which included patients with blood potassium levels from 5.0 mmol/L to 5.5 mmol/L — to clinical care is unclear. Moreover, there is no clinical evidence that sodium zirconium cyclosilicate improves survival, cardiovascular and renal outcomes, improves quality of life, or allows clinicians to optimize RAASi therapies in patients who require these medications.
- Results of subgroup analyses were difficult to interpret because of limitations such as the lack of stratification of randomization by subgroup categories and post-hoc analysis in specific subgroups of interest (e.g., eGFR < 30 mL/min/1.73 $m^2$, RAASi use).
- The absence of comparative data was considered a key limitation of the evidence base for sodium zirconium cyclosilicate. CDEC noted that the sponsor attempted to conduct an RCT comparing sodium zirconium cyclosilicate with sodium polystyrene sulfonate, but the trial was terminated early by an independent Data Safety Monitoring Board due to safety concerns with sodium polystyrene sulfonate. Further details about this trial were unavailable. RCTs comparing sodium zirconium cyclosilicate with other relevant comparators are not presently available.
- Sodium zirconium cyclosilicate has been associated with edema-related adverse events, including fluid overload (hypervolemia), and generalized and peripheral edema. CDEC discussed that the Health Canada review reported a higher incidence of edema with sodium zirconium cyclosilicate (i.e., 1.8% with 5 g, 5.3% for 10 g, and 14.3% for 15 g versus 1.7% with placebo), though it was noted that the review indicated that 53% of edema cases were managed with a diuretic or adjusting diuretic dose, with the remainder not requiring any treatment. Nevertheless, CDEC considered these to be important events in the patient population most likely to receive the drug (i.e., those with heart failure, chronic kidney disease, and diabetes mellitus).
- The long-term safety of sodium zirconium cyclosilicate is unknown. The reviewed RCTs ranged from two to eight weeks in duration. Two longer-term extension studies (ZS-004E and ZS-005) provided safety data up to 12 months; however, these

studies were single-arm, open-label studies, with selective patient populations. Data from the extension-studies were also limited by discontinuation rates of 35.8% in ZS-004E and 37.5% in ZS-005. These points make it difficult to interpret the safety results from the extension studies.

- CDEC could not determine the cost-effectiveness of sodium zirconium cyclosilicate, due in part to the uncertainty in the clinical evidence.

## Background

Sodium zirconium cyclosilicate has a Health Canada indication for the treatment of hyperkalemia in adults. Sodium zirconium cyclosilicate is a microporous zirconium silicate with a specific crystal geometry that reduces potassium by selectively binding to potassium ions in the gut in exchange for sodium and hydrogen ions. It is available as a powder in 5 g or 10 g sachets that is dissolved in water for an oral suspension. The recommended starting dose for patients whose serum potassium level is > 5.0 mmol/L (correction phase) is 10 g administered three times a day as an oral suspension for up to two days. For continued maintenance treatment in patients who achieve normokalemia, a dose of 5 g daily is recommended, with possible titration up to 10 g once daily or down to 5 g once every other day, as needed. No more than 10 g daily should be used for maintenance therapy.

## Summary of Evidence Considered by CDEC

CDEC considered the following information prepared by the Common Drug Review (CDR): a systematic review of RCTs of sodium zirconium cyclosilicate and a critique of the manufacturer's pharmacoeconomic evaluation. The committee also considered input from clinical experts with experience in treating adults with hyperkalemia, and patient group–submitted information about outcomes and issues important to patients.

### Summary of Patient Input

Two patient groups, The Kidney Foundation of Canada and Diabetes Canada, provided combined input for this submission. Patient perspectives were obtained from an online survey that included seven patients living with chronic kidney disease (CKD) and four with diabetes. The following is a summary of key input from the perspective of the patient groups:

- Regulating potassium level is a concern for patients with CKD, particularly for those undergoing dialysis. This can be accomplished in part through lifestyle changes; however, patients described these changes as being highly restrictive to the point of having a negative impact on quality of life.
- Two patients reported having experience with sodium polystyrene sulfonate, a potassium binder, for hyperkalemia. They indicated dislike for the texture and taste of the medication and a desire to have it available in pill form.
- Most respondents identified that the following symptoms and concerns were important or very important to them: tiredness, interference with sleep, edema of the foot, effect on mood, interference with other medications, changes in appetite, cost, and length of time on the medication.
- Patients also noted concern for side effects and efficacy of the drug as other important factors when choosing a new medication for CKD.

### Clinical Trials

The systematic review included five double-blind, RCTs (three two-phase studies [ZS-003, ZS-004 and ZS-D9480], one acute phase study [ZS-D9482] and one maintenance phase study [DIALIZE]). In all three two-phase studies (i.e., ZS-003, ZS-004 and ZS-D9480) patients were required to achieve normokalemia (serum potassium 3.5 mmol/L to 5.0 mmol/L) upon completion of the acute phase to be eligible for entering the maintenance phase. In all five included studies, patients treated with sodium polystyrene sulfonate within the last seven days before screening were excluded. The DIALIZE study was the only study of patients with end-stage kidney disease and on dialysis.

ZS-003 included 754 adult patients (> 18 years of age) with mild to moderate hyperkalemia (serum potassium 5.0 mmol/L to 6.5 mmol/L). Patients were randomized in a 1:1:1:1:1 ratio to placebo or sodium zirconium cyclosilicate 1.25 g, 2.5 g, 5 g, or 10 g three times daily for the first 48 hours (days 1 to 2); however the 1.25 g and 2.5 g doses were not included in the CDR review as they

are not part of Health Canada's approved dosing regimen. Patients who were normokalemic (3.5 mmol/L – 5.0 mmol/L) after 48 hours were randomized in a 1:1 ratio to the same acute phase dose or placebo administered once daily for 12 days (days 3 to 14). The end of study assessment occurred seven days after the last dose of study drug (day 21 for patients enrolled in the maintenance phase, otherwise day 9 for patients not enrolled in the maintenance phase).

ZS-004, also known as HARMONIZE, consisted of two phases, with an open-label acute phase of two days followed by a randomized 28-day maintenance phase. Patients were randomized in a 7:4:4:4 ratio to placebo, sodium zirconium cyclosilicate 5 g, 10 g, or 15 g once daily for 28 days. The 15 g dose is not included in this review as it is not approved by Health Canada. A total of 258 adult patients (> 18 years of age) with serum potassium of 5.1 mmol/L or greater at screening were included and entered the open-label 48-hour acute phase and received sodium zirconium cyclosilicate 10 g three times daily. Patients were eligible to enter the maintenance phase if they achieved normokalemia after 48 hours. Patients who completed the maintenance phase or who discontinued due to hypo- or hyperkalemia were offered participation in an open-label extension study (ZS-004E) to evaluate long-term safety and efficacy of sodium zirconium cyclosilicate. Patients who did not enter ZS-004E were followed for seven days after the last dose of study drug for end of study (day 35).

ZS-D9480, also known as HARMONIZE Global, has a similar design to ZS-004. A total of 267 adult patients (18 to 90 years of age) with two consecutive serum potassium values of 5.1 mmol/L or greater entered the acute phase, in which patients were administered sodium zirconium cyclosilicate 10 g three times daily for 48 hours. If patients achieved normokalemia after the acute phase, they were eligible to enter a 28-day maintenance phase, in which they were randomized in a 1:2:2 ratio to placebo, sodium zirconium cyclosilicate 5 g, or sodium zirconium cyclosilicate 10 g once daily (N = 248). An end of study assessment occurred seven days after the last dose of study drug (day 35).

ZS-D9482 is a phase II/III study that was conducted during the acute phase in 103 Japanese patients 18 years of age or older with two consecutive i-STAT serum potassium values of 5.1 mmol/L to 6.5 mmol/L, inclusive. Patients were randomized in a 1:1:1 ratio to placebo, sodium zirconium cyclosilicate 5 g, or 10 g three times daily for 48 hours. The 5 g dose is not included in this review as it is not approved by Health Canada for the acute phase. Patients were followed for seven days after the last dose (day 9).

DIALIZE is a phase IIIb study that included patients with end-stage renal disease (ESRD) who were being managed with hemodialysis three times a week. The treatment period was eight weeks, with an initial four-week dose titration period followed by a four-week stable dose period, during which efficacy was evaluated. A total of 196 patients were randomized in a 1:1 ratio to placebo or a starting dose of sodium zirconium cyclosilicate 5 g once daily, administered on non-dialysis days. The dose was titrated in 5 g increments, to a maximum of 15 g once daily, to maintain normokalemia (i.e., pre-dialysis serum potassium 4.0 mmol/L – 5.0 mmol/L). Patients were followed for two weeks after the last dose of study drug.

## Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

Acute phase

- Change in serum potassium
- Time to normalization (3.5 mmol/L to 5.0 mmol/L)
- Time to first potassium decrease of 0.5 mmol/L
- Proportion of patients who achieved potassium normalization at the end of 24 and 48 hours
- Exponential rate of change in serum potassium in the initial 48 hours of treatment
- Change in potassium from baseline
- Exponential rate of change in potassium during the first 24 hours

Maintenance phase

- Exponential rate of change over the duration of the maintenance phase

- Time to relapse (i.e., return to potassium baseline value)
- Number of days remaining normokalemic
- Proportion of patients who retained normal potassium levels at the end of the subacute phase
- Change in potassium from baseline
- Time to potassium increase of 0.5 mmol/L
- Least square mean of all serum potassium values
- Time to hyperkalemia (potassium ≥ 5.1 mmol/L)
- Proportion of patients who remained normokalemic

Harms

- Adverse events, serious adverse events (SAEs), withdrawal due to adverse events (WDAEs), hypokalemia, edema, gastrointestinal upset (including constipation and bowel obstruction)

ZS-D9480 additionally evaluated health-related quality of life with the EuroQol 5-Dimension, 5 Levels (EQ-5D-5L) at day 1 of the acute phase and at end of the maintenance phase. Hospitalizations and emergency room visits were evaluated in ZS-004 only. Further, continuation or need for discontinuation of RAASi or mineralocorticoid receptor antagonist treatment at regular doses was considered where data were available; however, none of the studies were designed to evaluate the effect of sodium zirconium cyclosilicate on RAASi or mineralocorticoid receptor antagonist therapies, and there were no protocol-defined specifications of what constituted changes in these therapies.

In ZS-003 and ZS-D9482, the primary outcome was the exponential rate of change in serum potassium in the initial 48 hours of the acute phase. In addition, the ZS-003 study also included the exponential rate of change in serum potassium over the 12 days of the maintenance phase. The primary outcome in ZS-004 and ZS-D9480 was the least square (LS) mean of all available serum potassium values during the maintenance phase (days 8 to 29). The primary outcome in DIALIZE was the proportion of patients who maintained a pre-dialysis serum potassium of 4.0 mmol/L to 5.0 mmol/L during at least three of four hemodialysis treatments after the long interdialytic interval and who did not require rescue therapy.

Data regarding survival, arrhythmia and major adverse cardiovascular events, and kidney disease and major adverse kidney events, as efficacy end points were included in the systematic review protocol, but not available in any of the included studies. However, they were presented in the harms section.

## Efficacy

***Acute Phase:***

The estimates for the acute phase outcomes that were tested as part of a sequential closed statistical testing procedure, to control for type I error. The primary outcome in Study ZS-003 (N = 301) and Study ZS-D9482 (N = 99), the exponential rate of potassium change over 48 hours, demonstrated that sodium zirconium cyclosilicate 10 g three times daily reduced serum potassium at a statistically significant ($P = 10^{-31}$ and $P < 0.0001$, respectively) higher rate compared with placebo. In ZS-003, the sodium zirconium cyclosilicate group had a 0.48 mmol/L greater decrease in serum potassium at 48 hours compared with placebo, and in ZS-D9482 about a 1 mmol/L greater decrease compared with placebo. The percentage of patients who achieved normokalemia (3.5 mmol/L to 5.0 mmol/L) at 48 hours was 86.4% with sodium zirconium cyclosilicate versus 47.8% with placebo in ZS-003, and 91.7% versus 15.2% in ZS-D9482.

***Maintenance Phase:***

Patients entered the maintenance phase if they achieved normokalemia after 48 hours of treatment in the acute phase. Estimates for the maintenance phase outcomes that were tested as part of a sequential closed statistical testing procedure, to control for type I error, were available for three of the four studies and have been summarized below.

*Exponential rate of change in serum potassium*

Across all four studies with a maintenance phase, a consistent effect in favour of sodium zirconium cyclosilicate was observed.

In ZS-003 (N = 256), the exponential rate of change in serum potassium over 28 days of treatment was smaller for sodium zirconium cyclosilicate 5 g and 10 g compared with their corresponding placebo groups (i.e., there was a greater degree of potassium stabilization.)

- sodium zirconium cyclosilicate 5 mg versus placebo: 0.0009 versus 0.0047, *P* = 0.0083
- sodium zirconium cyclosilicate 10 mg versus placebo: 0.00137 versus 0.01039, *P* < 0.0001

*Mean serum potassium through days 8 to 29*

In Study ZS-004 (N = 181), the mean (95% CI) serum potassium through days 8 to 29 was lower for sodium zirconium cyclosilicate 5 g and 10 g compared with placebo.

- Placebo, 5.1 mmol/L (5.0 to 5.2)
- Sodium zirconium cyclosilicate 5 g, 4.8 mmol/L (4.6 to 4.9), *P* = 0.0001 versus placebo
- Sodium zirconium cyclosilicate 10 g, 4.5 mmol/L (4.4, 4.6), *P* < 0.0001 versus placebo

Study ZS-D9480 (N = 248) also found lower mean (SE) of serum potassium through days 8 to 29 for 5 g and 10 g compared with placebo.

- LS MEAN (95% CI) difference: sodium zirconium cyclosilicate 5 g versus placebo = 0.90 (0.88 to 0.93)
- LS MEAN (95% CI) difference: sodium zirconium cyclosilicate 10 g versus placebo = 0.82 (0.80 to 0.85)

*Number of normokalemic days on day 29*

In Study ZS-004 (N = 181), the mean (standard error [SE]) number of normokalemic days was greater among the groups receiving sodium zirconium cyclosilicate compared with placebo.

- Placebo, 7.4 (8.0)
- Sodium zirconium cyclosilicate 5 g, 13.4 (7.6), *P* = 0.0001 versus placebo
- Sodium zirconium cyclosilicate 10 g, 13.9 (7.9), *P* < 0.0001 versus placebo

In Study ZS-D9480 (N = 248), the LS MEAN (SE) number of normokalemic days was also was greater among the groups receiving sodium zirconium cyclosilicate compared with placebo.

- Placebo, 3.5 (1.4)
- sodium zirconium cyclosilicate 5 g, 10.8 (1.1), *P* < 0.001 versus placebo
- sodium zirconium cyclosilicate 10 g, 15.6 (1.1), *P* < 0.001 versus , placebo

In Study ZS-004, more patients in both dose groups remained normokalemic at day 29 (71.1% of sodium zirconium cyclosilicate 5 g group and 76.0% of sodium zirconium cyclosilicate 10 g group) compared with placebo (47.6%). At day 35 (end of study), 63.6% and 48.1% of patients who received sodium zirconium cyclosilicate 5 g and sodium zirconium cyclosilicate 10 g, respectively, and 51.6% of patients who received placebo, remained normokalemic.

In Study SZ-D9480, more patients in both dose groups achieved normokalemia at day 29 (58.6% of sodium zirconium cyclosilicate 5 g group and 77.3% of the sodium zirconium cyclosilicate 10 g group) compared with placebo (24.0%, *P* < 0.001 compared with placebo for groups).

All studies conducted exploratory analyses of subgroups, such as patients with CKD, heart failure, and use of RAASi, and found effects in favour of sodium zirconium cyclosilicate. Yet, there was uncertainty as to whether patients with CKD and

eGFR < 30 mL/min/1.73m$^2$ would have similar beneficial effect and harm profile compared with other patients with eGFR equal to 30 mL/min/1.73m$^2$ or above. For the dialysis population in the DIALIZE study, more patients who received sodium zirconium cyclosilicate maintained a pre-dialysis serum potassium of 4.0 to 5.0 mmol/L and did not require rescue therapy compared with placebo (41.2% versus 1.0%, *P* < 0.001). There was limited data available for outcomes of interest to patients and clinicians, such as cardiac or renal morbidity, quality of life, or maintenance of RAASi or mineralocorticoid receptor antagonist therapies at optimal doses.

## Harms (Safety)

***Acute phase:***

In the 48-hour acute phase of ZS-003, ZS-004, ZS-D9480, and ZS-D9482, the more frequent (> 1%) adverse events were constipation, diarrhea, vomiting, and edema. There were a total of three WDAE in patients who received sodium zirconium cyclosilicate. No patient who received sodium zirconium cyclosilicate had a SAE and there were no deaths. Of the notable harms, constipation, edema, hypokalemia, atrial fibrillation, palpitations, hypertension, ventricular extrasystoles were slightly more common with sodium zirconium cyclosilicate compared with placebo. One patient in an open-label acute phase experienced intestinal obstruction.

***Maintenance phase:***

Across three studies (ZS-003, ZS-004, and ZS-D9480), SAEs were experienced by six patients who received sodium zirconium cyclosilicate 10 g and 12 patients who received sodium zirconium cyclosilicate 5 g, and four patients who received placebo. There were eight patients with WDAE in the 10 g group, 14 in the 5 g group, and four in placebo. In DIALIZE, SAEs were experienced by seven patients on sodium zirconium cyclosilicate and eight patients on placebo. There were a total of three deaths in the maintenance phase across the four studies. One patient who received sodium zirconium cyclosilicate 5 g died from respiratory distress, one patient receiving 10 g died of myocardial infarction, and one patient on dialysis in the DIALIZE study who received sodium zirconium cyclosilicate died of peripheral arterial occlusive disease.

Of the notable harms, constipation was more frequent with sodium zirconium cyclosilicate 10 g. One patient on 5 g had small intestinal obstruction. Edema and/or peripheral edema were observed in most studies: 20 patients in the 10 g groups, six patients in the 5 g groups, and four patients in the placebo groups. Hypokalemia was observed more frequently with higher doses of sodium zirconium cyclosilicate. In ZS-004, hypokalemia occurred in eight patients in the 10 g group, and none in placebo or 5 g. In ZS-D9480, one patient experienced hypokalemia in the 10 g group, and there were no cases in placebo or 5 g groups. In DIALIZE, five patients in both the placebo and sodium zirconium cyclosilicate groups experienced pre-dialysis hypokalemia.

Two additional studies, ZS-004E and ZS-005, provided longer term safety and efficacy data for sodium zirconium cyclosilicate. During the extended dosing phases of ZS-004E and ZS-005, 66.7% and 65.5% of patients reported an AE, 19.5% and 21.6% reported a SAE, 8.9% and 13.7% reported a WDAE, respectively. Eight (1.1%) deaths were reported in ZS-005, none of which were considered related to the study drug. Hypertension, peripheral edema, and gastrointestinal disorders (i.e., constipation, vomiting, and diarrhea) were some of the most frequently occurring adverse events in the two studies, and notable harms for this review.

## Indirect Treatment Comparisons

No indirect comparisons were available for consideration.

## Cost and Cost-Effectiveness

At the submitted price of $12.50 per 5 g and $25 per 10 g sachet, at the recommended dose of 10 g three times a day during the correction phase, sodium zirconium cyclosilicate costs $75 daily. The average annual cost of sodium zirconium cyclosilicate for maintenance treatment ranges from $2,283 to $9,131 per patient (or $6.25 to $25 daily).

The manufacturer submitted a cost-utility analysis comparing sodium zirconium cyclosilicate with best supportive care (BSC), which included the intermittent use of sodium polystyrene sulfonate or calcium polystyrene sulfonate for the correction of potassium and lifestyle interventions for the maintenance of potassium levels. The manufacturer considered two distinct populations in their

economic evaluation the corrective treatment of hyperkalemia in adult patients; acute corrective treatment and maintenance treatment of hyperkalemia in adult CKD patients with an eGFR of < 30 mL/min/1.73 $m^2$, that have had at least two hyperkalemia events and are required to be suboptimally managed on RAASi. The primary analysis reflected a population of adult patients with hyperkalemia and an underlying condition of advanced CKD and/or heart failure. The manufacturer's base case model was conducted from the perspective of the Canadian publicly funded health care payer over a lifetime horizon (up to a maximum age of 100 years). In the model, patients transition between heart failure and CKD states and may experience worsening of kidney function, and transition to end-stage renal disease and initiate renal replacement therapy. Clinical trial data from studies ZS-004E and ZS-005 was used to inform treatment-specific potassium profiles. Patients were assumed to experience a hyperkalemia event when potassium levels exceed a defined threshold (5.5 mmol/L). Major adverse cardiac events, hospitalization, changes in RAASi use and mortality were dependent on potassium levels. The manufacturer assumed that patients who started treatment on sodium zirconium cyclosilicate will move onto BSC if they discontinue their initial treatment. Re-initiation was allowed after the first 28-day period and before renal replacement therapy initiation. The manufacturer reported incremental cost-utility ratios (ICURs) were $82,067 per quality-adjusted life-year (QALY) for corrective treatment and $83,693 per QALY for maintenance treatment, when sodium zirconium cyclosilicate is compared with BSC.

CADTH identified the following key limitations of the manufacturer's submitted economic analysis:

- The manufacturer requested listing sodium zirconium cyclosilicate for maintenance treatment of hyperkalemia in adults with CKD, with an eGFR of < 30 mL/min/1.73 m2 who had experienced two hyperkalemic episodes and were suboptimally managed on RAASi therapy. The clinical trial data used to inform the model includes patients with eGFR>30 mL/min/1.73 m2 and is not consistent with the reimbursement request. Therefore, the clinical effects of sodium zirconium cyclosilicate in the reimbursement request population, and as a result the cost-effectiveness, is unknown.
- The manufacturer assumed BSC consisted of intermittent use of sodium polystyrene sulfonate/calcium polystyrene sulfonate for the correction of potassium levels, and lifestyle interventions for the maintenance of normokalemia. The current standard of care in Canada consists of the use of loop diuretics in addition to sodium polystyrene sulfonate/calcium polystyrene sulfonate for hyperkalemia correction, and adjustment of concomitant medication specifically RAASi down titration or discontinuation as maintenance. Furthermore, the effectiveness of BSC in the economic maintenance model was based on response observed from the placebo arms of the clinical studies. Therefore, the comparators included in the economic model and their efficacy do not reflect current BSC in Canada.
- Despite the relationship between RAASi treatment and potassium levels being well established in the literature and by clinical experts, the effect of RAASi use on serum potassium levels was not modelled.
- Heart failure mortality rates were based on heart failure patients who previously experienced myocardial infarction. Mortality estimates from a general population of chronic heart failure patients would be more appropriate.
- Utility values were derived from a time trade-off questionnaire according to CKD stage, however preference-based EQ-5D values are available and considered to be a more appropriate source.
- The lowest cost for sodium polystyrene sulfonate should have been considered.
- The submitted model lacked transparency and was overly complex. This made both the assessment of validity and the ability to conduct reanalysis challenging.

To account for the above limitations, CADTH considered: using updated utility values for CKD stages, applying more appropriate mortality rates for heart failure patients, and, excluding the cost of sodium polystyrene sulfonate/calcium polystyrene sulfonate for BSC. CADTH estimated that for corrective treatment, the ICUR for sodium zirconium cyclosilicate is $187,924 per QALY when compared with no treatment; a price reduction of approximately 90% is required for sodium zirconium cyclosilicate to be the cost-effective intervention at a willingness-to-pay threshold of $50,000 per QALY. For maintenance treatment, the ICUR for sodium zirconium cyclosilicate is $106,137 per QALY when compared with no treatment; a price reduction of approximately 85% is required for sodium zirconium cyclosilicate to be the cost-effective intervention at a willingness-to-pay threshold of $50,000 per QALY.

## CDEC Members

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

## October 16, 2019 Meeting (Initial)

## Regrets

Two CDEC members.

## Conflicts of Interest

None

## March 18, 2020 Meeting (Reconsideration)

## Regrets

One CDEC member.

## Conflicts of Interest

None