CADTH

CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

SODIUM ZIRCONIUM CYCLOSILICATE (LOKELMA)

(AstraZeneca Canada Inc.)

Indication: For the treatment of hyperkalemia in adult patients.

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CADTH

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.

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Abbreviations

AE	adverse event
BSC	best supportive care
CDR	CADTH Common Drug Review
CKD	chronic kidney disease
CPS	calcium polystyrene sulfonate
eGFR	estimated glomerular filtration rate
EQ-5D	EuroQol 5-Dimensions
HF	heart failure
ICER	incremental cost-effectiveness ratio
MACE	major adverse cardiac event
NYHA	New York Heart Association
QALY	quality-adjusted life-year
RAASi	renin-angiotensin-aldosterone system inhibitor
RRT	renal replacement therapy
SPS	sodium polystyrene sulfonate
SZC	sodium zirconium cyclosilicate

Table 1: Summary of the Sponsor's Economic Submission

Drug product	Sodium zirconium cyclosilicate (Lokelma)
Study question	Is sodium zirconium cyclosilicate (SZC) a cost-effective alternative to best supportive care for the correction or normalization of serum potassium levels in patients with hyperkalemia?
Type of economic evaluation	Cost-utility analysis
Target population	Adults (age 18 years or older) with hyperkalemia and an underlying condition of advanced chronic kidney disease and/or heart failure
Treatment	• Correction treatment: For patients whose serum potassium level is > 5.0 mmol/L, the recommended starting dose of SZC is 10 g three times a day for up to 48 hours until normokalemia is achieved. • Maintenance treatment: For continued maintenance treatment to prevent recurrence of hyperkalemia, 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.
Outcome	Quality-adjusted life-years
Comparator	BSC, defined as intermittent use of SPS or CPS
Perspective	Canadian public health care payer
Time horizon	Lifetime (to a maximum age of 100 years)
Results for base case	The ICER for SZC vs. BSC: • Acute correction: $82,067 per QALY • Maintenance of normokalemia: $83,693 per QALY
Key limitations	CADTH identified the following key limitations: • The sponsor requested that SZC be listed for the maintenance treatment of hyperkalemia in adult CKD patients with an eGFR < 30 mL/min/1.73m^2. However, the clinical trial data used to inform the model include patients with eGFR > 30 mL/min/1.73m^2 and are not consistent with the reimbursement request. Therefore, the clinical effects of SZC in the reimbursement request population — and as a result, its cost-effectiveness — is unknown. • The sponsor assumed BSC consisted of intermittent use of SPS/CPS for the correction of serum potassium levels and lifestyle interventions for the maintenance of normokalemia. However, current standard of care in Canada consists of the use of loop diuretics in addition to SPS/CPS for hyperkalemia correction, and 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 SERUM POTASSIUM levels being well established in the literature and by clinical experts, the effect of RAASi use on SERUM POTASSIUM levels was not modelled. • HF mortality rates were based on patients with HF who had previously experienced myocardial infarction. Mortality estimates from a general population of patients with chronic HF would have been 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 a more appropriate source. • The lowest cost for SPS should have been considered.

CDR estimate(s)	• The submitted model lacked transparency and was overly complex. This made both the assessment of validity and the ability to conduct reanalysis challenging.
	CADTH addressed these limitations, where possible, using updated utility values for CKD stages; applied more appropriate mortality rates for HF patients; and excluded the cost of SPS/CPS for BSC. As such, BSC consists of no treatment in the CADTH base case. Based on CADTH reanalyses for: • Acute correction: the ICER for SZC is $187,924 per QALY when compared with no treatment. A price reduction of approximately 90% is required for SZC to be the cost-effective intervention at a willingness-to-pay threshold of $50,000 per QALY. • Maintenance of normokalemia: the ICER for SZC is $106,137 per QALY when compared with no treatment. A price reduction of approximately 85% is required for SZC to be the cost-effective intervention at a willingness-to-pay threshold of $50,000 per QALY.

BSC = best supportive care; CDR = CADTH Common Drug Review; CKD = chronic kidney disease; CPS = calcium polystyrene sulfonate; HF = heart failure; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; RAASi = renin-angiotensin-aldosterone system inhibitor; SPS = sodium polystyrene sulfonate; SZC = sodium zirconium cyclosilicate; vs. = versus.

Drug	Sodium zirconium cyclosilicate (Lokelma)
Indication	Treatment of hyperkalemia in adults
Reimbursement request	Corrective treatment of hyperkalemia in adults Maintenance treatment of hyperkalemia in adults with chronic kidney disease (CKD) with an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 who have experienced at least 2 hyperkalemic events and are sub-optimally managed on renin-angiotensin-aldosterone system inhibitor (RAASi) therapy
Dosage form	5 g or 10 g powder for oral suspension
NOC date	July 25, 2019
Sponsor	AstraZeneca Canada Inc.

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; NOC = notice of compliance; RAASi = renin-angiotensin-aldosterone system inhibitor.

Executive Summary

Background

Sodium zirconium cyclosilicate (SZC) (Lokelma) is a non-absorbed, non-polymer inorganic powder with a uniform micropore structure that preferentially captures potassium in exchange for hydrogen and sodium cations. It is indicated for the treatment of hyperkalemia in adult patients. 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 (in water) for up to two days. For continued maintenance treatment, 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.[1] The sponsor submitted a price for SZC of $12.50 per 5 g and $25.00 per 10 g sachet.[2] At the recommended dose of 10 g three times a day during the correction phase, SZC costs $75 daily. The average annual cost of SZC for maintenance treatment ranges from $2,283 to $9,131 per patient ($6.25 to $25 daily).

The sponsor submitted a cost-utility analysis comparing SZC with best supportive care (BSC), which included the intermittent use of sodium polystyrene sulfonate (SPS) or calcium polystyrene sulfonate (CPS) for the correction of serum potassium levels as well as lifestyle interventions for the maintenance of serum potassium levels.[2] The sponsor considered two distinct populations in its economic evaluation: 1) adult patients with hyperkalemia who require corrective treatment; and, 2) adult patients requiring maintenance treatment who have chronic kidney disease (CKD), an estimated glomerular filtration rate (eGFR) of < 30 mL/min/1.73m^2, a history of at least two hyperkalemia events, and who are required to be suboptimally managed on renin-angiotensin-aldosterone system inhibitor (RAASi) therapies. The primary analysis reflected a population of adult patients with hyperkalemia and an underlying condition of advanced CKD and/or heart failure (HF), with scenario analyses focusing on a CKD-only and an HF-only population. The sponsor'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). Future costs and benefits were discounted at 1.5% per annum.

In the model, patients transition between HF and CKD states. They may also experience worsening of kidney function, transition to end-stage renal disease, and initiate renal replacement therapy (RRT). Patients were assumed to experience a hyperkalemia event when their serum potassium levels exceeded a defined threshold (5.5 mmol/L). Major adverse cardiac events (MACEs), hospitalization, changes in RAASi use, and mortality were dependent on serum potassium levels. The sponsor assumed that patients who started treatment on SZC would move on to BSC if they discontinued their initial treatment. Re-initiation was allowed after the first 28-day period and prior to RRT initiation. Both CKD and HF progression were based on the literature,[3,4] and a mixed-effects regression model based on clinical trial data was used to inform treatment-specific serum potassium profiles. Utility values were obtained from the literature.

The sponsor reported that SZC was associated with both more costs (increases of $663 for acute correction and $28,719 for maintenance) and quality-adjusted life-years (QALYs) than BSC (0.008 more QALYs for acute correction and 0.343 more QALYs for maintenance). The resulting incremental cost-effectiveness ratios (ICERs) were $82,067 per QALY for acute correction and $83,693 per QALY for maintenance.

Summary of Identified Limitations and Key Results

CADTH identified several key limitations with the model submitted by the sponsor. Primarily, the reimbursement request for SZC for the maintenance treatment of hyperkalemia in adult CKD patients with an eGFR of < 30 mL/min/1.73m^2 who have had at least two hyperkalemia events is not reflected in the clinical trials, as they included patients with eGFRs > 30 mL/min/1.73m^2 (patients in studies ZS-004E and ZS-005 had mean eGFRs of 36.08 and 35.53, respectively). Additionally, the clinical data were not stratified according to the number of previous hyperkalemia events. Therefore, the data used to inform the model are not consistent with the reimbursement request, as they may be more reflective of a broader population. Furthermore, despite the relationship between RAASi treatment and serum potassium levels being well established in the literature and by clinical experts, the sponsor did not model the effect of change in RAASi use on serum potassium and did not provide justification for this omission. This omission likely favours SZC, as more patients will remain on RAASi therapies. Unfortunately, these limitations could not be addressed through reanalysis of the model due to lack of data and inflexibility of the model structure.

The sponsor assumed that BSC consisted of intermittent use of SPS or CPS for the correction of serum potassium levels and lifestyle interventions for the maintenance of normokalemia. However, in clinical practice, patients would receive a diuretic in addition to SPS or CPS during a hyperkalemia event, and would either discontinue or receive a reduced dose of RAASi to avoid future hyperkalemia events. These strategies were not evaluated in the economic model. Moreover, the effectiveness of BSC in the economic maintenance model is based on the placebo response in the clinical trials, which is not reflective of management with BSC. The HF mortality rates used were from a source that explored mortality in HF patients following myocardial infarction.[5] Mortality data from a cross-section of HF patients would be more appropriate.[6] Finally, CADTH guidelines recommend that the utilities be obtained from a generic classification system, such as the EuroQol 5-Dimensions (EQ-5D) questionnaire; however, the sponsor's source of utilities was based on a time trade-off questionnaire.[7]

CADTH Common Drug Review (CDR) addressed these issues in its base case by using utility values from Jesky et al.[8] and mortality rates in the HF population from Aldahl et al.,[6] and by excluding SPS or CPS treatment costs associated with BSC. As such, BSC consists of no treatment in the CADTH base case. Exploratory analyses were conducted by CADTH to assess the potential cost-effectiveness of SZC in a population of patients with CK only, patients with HF only, and patients with CK and HF. Additionally, alternative SZC treatment durations in the correction phase were explored in scenario analyses. Finally, a generic SPS product became available in Canada at the time of the review; therefore, the inclusion of SPS treatment costs using the lowest-cost product was also explored in a scenario analysis.

Conclusions

In CADTH's base case, SZC was associated with an ICER of $187,924 per QALY gained compared with no treatment for acute correction of hyperkalemia. For acute correction, a price reduction of approximately 90% was required to achieve an ICER below $50,000 per QALY. For maintenance treatment in a population similar to those in the clinical trials, SZC was associated with an ICER of $106,137 per QALY gained compared with BSC, where a price reduction of approximately 85% was required to achieve an ICER below $50,000 per QALY.

Given the limitations of the clinical data and submitted model structure, the results should be viewed with caution, especially when considering the potential impact of SZC on maintenance of normokalemia in the reimbursement request population. There is significant uncertainty in the effects of treatment with SZC in patients with eGFR < 30 mL/min/1.73m^2 as per the reimbursement request.

Information on the Pharmacoeconomic Submission

Summary of the Sponsor's Pharmacoeconomic Submission

The sponsor submitted a cost-utility analysis comparing SZC with BSC for the treatment of hyperkalemia.[2] Analysis was conducted for two distinct populations: adult patients requiring 1) corrective treatment of hyperkalemia; and, 2) maintenance treatment who have CKD, an estimated glomerular filtration rate (eGFR) of < 30 mL/min/1.73m^2, a history of at least two hyperkalemia events, and who are required to be suboptimally managed on RAASi therapies. The sponsor incorporated a discount rate of 1.5% per annum and conducted the analysis from the perspective of the Canadian publicly funded health care system , with a lifetime horizon to a maximum age of 100 years.

A patient-level simulation model was developed in Microsoft Excel to simulate the disease course of adult patients with hyperkalemia and an underlying condition of advanced CKD (non-dialysis CKD stage 3a to stage 5 categorized through the decline of eGFR) and/or HF (New York Heart Association [NYHA] functional class I, II, II, or IV). The model used a four-week cycle length; however, shorter cycle lengths (one to 14 days) were chosen for the first cycle in order to capture the changes in serum potassium levels during the corrective phase. The model included a cohort of patients with CKD and/or HF using the combined studies ZS-004E and ZS-005,[9,10] which had similar baseline characteristics and physiological parameters.

All patients in the model started in a health state according to CKD stage 3b and NYHA functional classes I to IV based on the patient population from the combined ZS-004E and ZS-005 studies.[10,11] Patients were assumed to experience one hyperkalemia event at the beginning of the simulation and possibly one additional event in each 28-day subsequent cycle. Hyperkalemia event severity is defined as high, medium, and low if serum potassium levels exceed the 6.5 mmol/L, 6.0 mmol/L, and 5.5 mmol/L thresholds, respectively. In each cycle, patients could transition between HF and CKD stages or enter the absorbing death state. Over time, patients could experience worsening of kidney function and transition to end-stage renal disease, where they would initiate RRT. Following RRT initiation, patients transition across dialysis, transplant health states, and death (Figure 1).

A mixed-effects regression model based on data from studies ZS-004 and ZS-005 was used to simulate treatment- and patient-specific serum potassium profiles. MACEs, hospitalization, changes in RAASi use, and mortality were dependent on serum potassium levels (Figure 2 and Figure 3 in Appendix 4). Potassium profiles were modelled until RRT initiation; only dialysis-related complications were modelled following RRT. Patients receiving RAASi at baseline were assumed to receive the maximum appropriate dose. In the first 28 days of the model, RAASi discontinuation and down-titration were not allowed for patients receiving SZC treatment; however, after the first 28-day cycle, a proportion of patients was assumed to discontinue or down-titrate RAASi treatment according to their serum potassium levels (Table 11). Treatment duration for SZC was limited to two days using a 10 g dose administered three times daily in the corrective phase, and four cycles using a 5 g daily dose in the maintenance phase, whereas treatment duration for BSC was limited to one cycle in both analyses. After the first 28-day period, it was assumed that patients who reached a very high (≥ 6.5 mmol/L) or very low (< 3.5 mmol/L) serum potassium level while on SZC treatment would discontinue treatment. Patients could also

discontinue SZC treatment due to lack of efficacy, problems with adherence, or adverse events (AEs). Upon discontinuation, patients were assumed to switch to BSC, which was assumed to consist of intermittent use of SPS or CPS for the correction of serum potassium levels and lifestyle interventions for maintenance (e.g., dietary interventions and modifications of concomitant medications). Patients could re-initiate treatment after the first 28-day period and prior to RRT initiation if their serum potassium level reached a defined threshold (5.5 mmol/L). Re-initiation of treatment could occur multiple times in the model.

The sponsor used risk equations to predict the occurrence of MACE in the HF population. Mortality in the HF population was implemented using the Seattle Heart Failure Model.[12] Published literature was used to inform MACE rates, CKD and HF disease progression, and mortality in the CKD population.[3,4] If the general population probability of death exceeded the estimated probability of death based on comorbidity, RAASi use, and serum potassium level, then the general population mortality was applied. Other model inputs, such as hospitalization, RAASi down-titration, or RAASi discontinuation were obtained from published literature.[13-15]

Rates of AEs for SZC treatment and BSC were based on trial values[10] and on the literature,[16] respectively. Each AE was assumed to require one visit to a specialist. The model included drug acquisition costs, costs of managing AEs, and costs related to acute hyperkalemia and disease (CKD and HF) management. Drug acquisition costs for SZC were provided by the sponsor, and treatment dosing was based on dose distributions from Study ZS-005.[10] Health care costs were taken from the medical literature and official sources, such as provincial formularies and schedules of benefits. A micro-costing approach based on physician surveys was adopted to estimate the cost of several parameters (refer to Table 12 and Table 13 in Appendix 4 for further costing details). Costs for RRT and AE management were excluded from the model. Health-state utilities for CKD, dialysis, transplant, HF and disutilities associated with MACE, hospitalization events, and dialysis complications were obtained from the literature.[7,17-20] Utility decrements for AEs were also obtained from the literature.[21-23] No disutility was assumed for an acute hyperkalemia event.

The progression of the cohort and the results is hard-coded as it is inputted though a series of Visual Basic macros. Due to a lack of transparency in the submitted model, CDR was unable to validate several model parameters.

Sponsor's Base Case

For the acute correction phase, the sponsor reported a probabilistic ICER of $82,067 per QALY gained for SZC versus BSC. Compared with BSC, SZC was both more effective (incremental QALYs of 0.008) and costly (incremental costs of $663), as shown in Table 15. Detailed cost information and a summary of predicted clinical outcomes can be found in Table 17 and Table 19 of Appendix 5. At a willingness-to-pay threshold of $100,000 per QALY, the probability of SZC being cost-effective compared to BSC was reported to be 68.6%.

For the maintenance of normokalemia, the sponsor reported a probabilistic ICER of $83,693 per QALY gained for SZC versus BSC. Compared with BSC, SZC was both more effective (incremental QALYs of 0.343) and costly (incremental costs: $28,719), as shown in Table 16. Detailed cost information and a summary of predicted clinical outcomes can be found in Table 18 and Table 20 of Appendix 5. At a willingness-to-pay threshold of $100,000 per QALY, the probability of SZC being cost-effective compared to BSC was reported to be 99.6%.

Summary of Sponsor's Sensitivity Analyses

The sponsor conducted probabilistic sensitivity analyses for both treatment phases. Scenario analyses were performed on the base case using 0% and 3% discounting. The sponsor conducted additional probabilistic analysis focusing on patients with CKD only and HF only (i.e., the sponsor base case focused on the CKD and/or HF populations).

In both populations, the results of the sponsor's scenario analysis exploring various discount rates led to findings similar to those in the base-case. In the correction phase, focusing on patients with CKD only and HF only decreased the ICERs for SZC to $64,086 and $64,099 respectively, whereas in the maintenance phase, focusing on patients with CKD only and HF only decreased the ICERs for SZC to $75,204 and $45,174 respectively.

Limitations of Sponsor's Submission

- **Clinical trial information does not reflect the requested reimbursement population:** The sponsor has requested that SZC be listed for the maintenance treatment of hyperkalemia in adult CKD patients with an eGFR of < 30 mL/min/1.73m^2 (corresponding to CKD stages 4 and 5) who have had at least two hyperkalemia events and required suboptimal management on RAASi. However, the data used to populate the base case were based on studies ZS-004E and ZS-005, which included CKD patients with eGFRs greater than 30 mL/min/1.73m^2 (patients in these studies had mean eGFRs of 36.08 and 35.53, respectively), corresponding to CKD stage3b, as well as patients with HF only (no CKD). Furthermore, the clinical data were not stratified according to the number of previous hyperkalemia events. As a result, the clinical data used in the model may not fully reflect the patient population that the sponsor is seeking reimbursement for; it may be more reflective of a broader population.

  Additionally, there is a lack of clinical efficacy and safety information for patients who are on dialysis. As such, the cost-effectiveness of SZC in this population is uncertain. CADTH was unable to address these limitations due to lack of clinical evidence regarding treatment effectiveness. However, CADTH conducted exploratory analyses on subgroups of patients with CKD only, patients with HF only, and patients with CKD and HF patients (based on subgroup analysis reported in the sponsor's pharmacoeconomic submission) to explore the cost-effectiveness of SZC in these populations.

- **Appropriateness of comparator:** The sponsor assumed that BSC consisted of intermittent use of SPS and CPS for the correction of serum potassium levels and lifestyle interventions for the maintenance of normokalemia. However, as per the clinical experts consulted by CDR, in clinical practice, patients would receive a loop diuretic in addition to SPS or CPS upon a hyperkalemia event, and would either discontinue or receive a reduced dose of RAASi to avoid future hyperkalemia events. There is a lack of head-to-head studies comparing SZC with current standard of care (consisting of either SPS or CPS use, lifestyle modifications, or RAASi modifications); therefore, the sponsor assumed the effectiveness of BSC during the maintenance phase to be equivalent to placebo, and the effectiveness of BSC during the corrective phase to be equivalent to the pooled placebo and SZC response, as observed in the clinical trials. The comparators included in the economic model and their efficacy do not reflect BSC received by patients in current clinical practice in Canada.

  CADTH was unable to fully address this limitation due to lack of clinical data and structural limitations in the model. However, CADTH excluded SPS or CPS costs from the BSC arm

in order to be consistent with the BSC efficacy based on the placebo assumption. As such, BSC consists of no treatment in the CADTH base case.

- **Inappropriate modelling of the relationship between RAASi treatment and serum potassium:** The effect of change in RAASi use on serum potassium was not included in the model. This was considered inappropriate by the clinical experts consulted by CADTH. Furthermore, the relationship between RAASi use and serum potassium levels has been well established in the literature.[24]

  The sponsor also assumed that only patients on BSC would discontinue or down-titrate RAASi treatment within the first 28 days of the model. This assumption was considered inappropriate by the clinical experts, as patients on SZC are also expected to discontinue RAASi treatment. Given the assumption that only patients on BSC discontinue RAASi in the first 28 days of the model, excluding the effect of RAASi discontinuation on serum potassium levels is likely to favour SZC, as the sponsor might be underestimating the effectiveness of BSC. Given the structure of the model, it was not feasible to explore alternate assumptions about the relationship between RAASi and serum potassium levels.
- **Source of mortality rates in HF patients:** Mortality rates were based on the study by Krogager et al. (2015),[5] which explored the mortality risk of serum potassium levels in patients with HF following myocardial infarction. This population does not reflect the general HF population, where lower rates of mortality are observed. The use of data from this specific population is not appropriate. A more recent publication by Aldahl et al. (2017)[6] assessed the risk of mortality in patients with chronic HF and was considered in the CADTH reanalyses.
- **Source of utilities:** In the sponsor's base case, utilities for CKD stages were derived by Gorodetskaya et al. (2005)[7] from a time trade-off questionnaire. As per CADTH guidelines,[25] utilities should be obtained from a generic classification system, such as the EQ-5D or Health Utilities Index; therefore, CADTH considered that the preference-based EQ-5D values derived from Jesky et al. (2016)[8] provided a more plausible set of utility values.
- **Exclusion of SPS generics price:** A generic SPS product (produced by Odan) became available in Canada at the time of the review. The sponsor's base case used the branded cost for SPS. The lowest cost for SPS was used in CADTH's base case.[25]
- **Lack of transparency and functionality of the sponsor's submitted model:** The submitted model had several issues that made validation and evaluation challenging. The coding used in the modelling was overly complicated and lacked transparency. The progression of the cohort is hard-coded as it is inputted though a series of Visual Basic macros, precluding an examination of how patients move from state to state. Furthermore, the model run-time ranged from five to six hours, which limited CADTH's ability to test scenarios.

CADTH Reanalyses

The CADTH reanalyses could not address structural limitations of the model, which does not correctly reflect the relationships between RAASi treatment, serum potassium, and current clinical practice.

CADTH reanalyses included the following changes to the sponsor's base case (see results in Table 2 and Table 3):

1. Mortality rates in HF population: Use of Aldahl et al. study
2. Source of utilities: Use of the Jesky et al. study
3. Cost of comparator: Exclude SPS/CPS costs for BSC (i.e., BSC consists of no treatment in the CADTH base case)
4. **CADTH base case (1 to 3)**

Scenario analyses using the CADTH base case:

4a. CADTH base case plus SPS costs using the generic product cost

4b. CADTH base case plus alternative corrective treatment duration scenario (one day)

4b. CADTH base case plus subgroups of patients with CKD only, patients with HF only, and patients with CKD and HF

Acute Correction

In CADTH's base-case analysis for the acute correction phase, SZC was associated with 0.008 additional QALYs and a $1,423 higher cost compared to BSC. The ICER for SZC was $187,924 per QALY when compared to no treatment (Table 2).

Exploratory scenario analyses were conducted using the CADTH base case to investigate the inclusion of SPS costs using the lowest available SPS cost and alternative corrective treatment duration. Including SPS costs resulted in an ICER of $144,781. Using a treatment duration of one day resulted in a lower incremental cost-effectiveness ratio (ICER; $110,608) compared to the CADTH base case ($187,924). Finally, additional subgroup analysis of the CKD-only, HF-only, and CKD and HF populations resulted in ICERs of $133,734, $178,759, and $180,799, respectively. Full results of the analysis are presented in Table 21 of Appendix 5.

Table 2: Results from CADTH Reanalyses: Acute Correction Phase

	Description	SZC vs. BSC (no treatment)		
		Incremental cost ($)	Incremental QALYs	ICER ($/QALY)
	Sponsor base case	**663**	**0.008**	**82,067**
1	Use of Aldahl et al. study as source of mortality rates in HF population	769	0.008	92,449
2	Use of Jesky et al. study as source of utilities	663	0.007	89,636
3	Exclude SPS/CPS costs for BSC	1,161	0.008	143,596
4	**CADTH base case (1 to 3)**	**1,423**	**0.008**	**187,924**
Scenario analyses of CADTH base case				
4a	Including SPS costs using the lowest available cost	1,097	0.008	144,781
4b	Alternative treatment duration (1 day)	838	0.008	110,608
4c	Subgroup of patients with CKD	1,595	0.012	133,734
4c	Subgroup of patients with HF only	1,428	0.008	178,759
4c	Subgroup of patients with HF + CKD	1,399	0.008	180,799

BSC = Best supportive care; CKD = chronic kidney disease; CPS = calcium polystyrene sulfonate; HF = heart failure; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SPS = sodium polystyrene sulfonate; SZC = sodium zirconium cyclosilicate; vs. = versus.

Low eGFR Maintenance of Normokalemia

In CADTH's base-case analysis for the maintenance of normokalemia, SZC was associated with an additional 0.228 QALYs and $24,204 in total costs compared to no treatment. The ICER for SZC was $106,137 per QALY when compared to no treatment (Table 3).

Exploratory scenario analyses were conducted using the CADTH base case to investigate the inclusion of SPS costs using the lowest available SPS cost and alternative corrective treatment duration. Including SPS costs resulted in an ICER of $103,835. Additional subgroup analysis of the CKD-only, HF-only, and CKD-plus-HF populations resulted in ICERs of $81,767, $54,252, and $107,433, respectively. Full results of the analysis can be found in Table 22 of Appendix 5.

Table 3: Results from CADTH Reanalyses: Maintenance of Normokalemia Phase

	Description	SZC vs. BSC (no treatment)		
		Incremental cost	Incremental QALYs	ICER ($/QALY)
	Sponsor base case	**28,719**	**0.343**	**83,693**
1	Use of Aldahl et al. study as source of mortality rates in HF population	23,154	0.244	95,035
2	Use of Jesky et al. study as source of utilities	28,719	0.316	90,862
3	Exclude SPS/CPS costs for BSC	29,487	0.343	85,930
4	**CADTH base case (1 to 3)**	**24,204**	**0.228**	**106,137**
Scenario analyses of CADTH base case				
4a	Including SPS costs using the lowest available cost	23,679	0.228	103,835
4c	Subgroup of patients with CKD only	14,241	0.174	81,767
4c	Subgroup of patients with HF only	25,060	0.460	54,525
4c	Subgroup of patients with HF + CKD	21,383	0.199	107,433

BSC = Best supportive care; CKD = chronic kidney disease; CPS = calcium polystyrene sulfonate; HF = heart failure; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SPS = sodium polystyrene sulfonate; SZC = sodium zirconium cyclosilicate; vs. = versus.

CADTH undertook a price-reduction analysis based on the sponsor-submitted and CADTH base-case analyses for both indications (corrective and maintenance). For the correction of hyperkalemia, price reductions of approximately 60% and 90% were required to achieve ICERs below $100,000 and $50,000 per QALY, respectively, compared with no treatment in the CADTH base case (Table 23). For the maintenance of normokalemia, price reductions of approximately 10% and 85% were required to achieve ICERs below $100,000 and $50,000 per QALY, respectively, compared with no treatment in the CADTH base case (Table 24).

Patient Input

Input was received from two patient groups: The Kidney Foundation of Canada and Diabetes Canada. According to the patient submission, managing serum potassium levels through dietary restriction is a treatment strategy commonly used for patients in the early stages of CKD and undergoing dialysis; however, this option does not work for all patients. Seventy-two percent of survey respondents reported having a dietary restriction, which was described as having a negative impact on their quality of life. Factors important to patients when selecting a medication included its impact on tiredness, interference with sleep, edema of the foot, effect on mood, contraindication with other medications, change in appetite, cost, and treatment duration. Additionally, patients expressed concerns about side effects and drug efficacy as other important factors when choosing a new medication for CKD. Survey respondents would like to see therapies for CKD that help them feel better and reduce the need for invasive therapies, such as surgery.

Based on the sponsor's economic model, only the impact of continued RAASi usage with SZC and quality of life with regards to CKD, HF, and AEs were explored. The negative impacts of dietary restrictions were not incorporated in the model, and SZC was associated with higher costs compared to current BSC.

Issues for Consideration

- There is considerable uncertainty in the clinical evidence. There are no trials comparing SZC to current standard of care in the correction or maintenance phases; as such, there is no clinical evidence that SZC is an alternative to dietary restrictions or to RAASi down-titration or discontinuation. Furthermore, there is no evidence of the impact of SZC on mortality, RAASi effectiveness, and RAASi discontinuation or re-initiation. These limitations introduce significant uncertainty into the model results.
- A novel non-absorbed, cation-exchange polymer (patiromer) has received Health Canada approval for the treatment of hyperkalemia in adults. The introduction of this comparator could affect the findings of the economic analysis.

Conclusions

When considering mortality rates from a general HF population and utilities based on the EQ-5D — and excluding the cost of treatments (SPS and CPS) — in CADTH's base case, SZC was associated with an ICER of $187,924 per QALY gained compared with no treatment for acute correction of hyperkalemia. A price reduction of approximately 90% was required to achieve an ICER below $50,000 per QALY. For maintenance treatment, SZC was associated with an ICER of $106,137 per QALY gained compared with no treatment for the acute maintenance of normokalemia, where a price reduction of approximately 85% was required to achieve an ICER below $50,000 per QALY.

It should be noted that given the limitations with the clinical data and the submitted model structure, the results should be viewed with caution, especially when considering the potential impact of SZC on maintenance of normokalemia in the reimbursement request population. There is significant uncertainty in the effects of treatment with SZC in patients with eGFR < 30 mL/min/1.73 m^2 as per the reimbursement request. Additionally, the cost-effectiveness of SZC in dialysis patients remains unknown.

Appendix 1: Cost-Comparison Table for Hyperkalemia

The comparators presented in Table 4 have been deemed appropriate by clinical experts. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are sponsor list prices unless otherwise specified. Existing Product Listing Agreements are not reflected in the table, and as such, may not represent the actual costs to public drug plans.

Table 4: CADTH Cost-Comparison Table for Hyperkalemia

Drug/comparator	Strength	Dosage form	Price ($)	Recommended daily dose	Average daily drug cost ($)	Average annual drug cost ($)
Sodium zirconium cyclosilicate (Lokelma)	**5 g 10 g**	**Powder**	**12.5000[a] 25.0000[a]**	**30 g[b] 2.5 g to 10 g[c]**	**75.00[b] 6.25 to 25.00[c]**	**2,283 to 9,131[c]**
Cation-exchange resin						
Sodium polystyrene sulfonate (generic)	454 g	Powder	42.0250	15 g to 60 g	1.39 to 5.55	507 to 2,029
Calcium polystyrene sulfonate (Resonium)	1 g	Powder	0.3865[d]	45 g to 60 g	17.39 to 23.19	6,353 to 8,470
Loop diuretics						
Furosemide (Lasix; generic)	10 mg/mL	Oral solution	0.3229	20 mg to 40 mg[e]	0.65 to 1.29	236 to 472
	10 mg/mL	Injectable solution	0.8650		1.73 to 3.46	632 to 1,264
	20 mg 40 mg 80 mg	Tab	0.0219 0.0327 0.0703[f]		0.02 to 0.03	8 to 12
Bumetanide (Burinex)	1 mg 5 mg	Tab	0.7907[d] 3.0184[d]		12.07 to 24.15	4,410 to 8,820
Ethacrynic acid (Edecrin)[e]	25 mg	Tab	0.9383[d]		0.94 to 1.88[g]	343 to 685[g]

Note: All prices are from the Ontario Drug Benefit Formulary (July 2019)[26] unless otherwise indicated, and do not include dispensing fees. Costs are based on 365.25 days per year.

Note: Cation-exchange resins are only expected to be utilized during the correction phase for the treatment of hyperkalemia. Although patiromer sorbitex calcium (Veltassa) is currently approved for use in Canada and considered a relevant comparator, no current pricing data are available. Pricing for 50 mg powder for injection is not currently available.

[a] Sponsor's submitted price.[2]

[b] Correction phase: 10 g administered three times a day.[1]

[c] Maintenance phase: recommended 5 g once daily. Titration up to 10 g once daily or down to 5 g once every other day as needed.[1]

[d] Saskatchewan Formulary (July 2019).[27]

[e] Dosing based on the publication by Rafique et al. (2019)[28] and the National Kidney Foundation: Best Practices in Managing Hyperkalemia in Chronic Kidney Disease.[29] The dosing of furosemide was assumed to be the same for other loop diuretics.

[f] Alberta Formulary (July 2019).[30]

[g] A dose range of 25 mg to 50 mg was applied for pricing for tablets and 50 mg for lyophilized powder used for injection.

Appendix 2: Summary of Key Outcomes

Table 5: When Considering Only Costs, Outcomes, and Quality of Life, How Attractive Is SZC Relative to BSC (CADTH Reanalyses)?

SZC versus BSC	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)				X		
Drug treatment costs alone				X		
Clinical outcomes			X			
Quality of life			X			
ICER or net benefit calculation[a]	Acute correction indication: $187,924 per QALY Maintenance of normokalemia indication: $106,137 per QALY					

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; NA = not applicable; SZC = sodium zirconium cyclosilicate.

[a] CADTH base case.

Appendix 3: Additional Information

Table 6: Submission Quality

	Yes/ good	Somewhat/ average	No/ poor
Are the methods and analysis clear and transparent?			X
Comments Reviewer to provide comments if checking "no"	The model lacks transparency.		
Was the material included (content) sufficient?		X	
Comments Reviewer to provide comments if checking "poor"			
Was the submission well organized and was information easy to locate?		X	
Comments Reviewer to provide comments if checking "poor"	None		

Table 7: Authors' Information

Authors of the pharmacoeconomic evaluation submitted to CADTH

☐ Adaptation of global model/Canadian model done by the sponsor

☒ Adaptation of global model/Canadian model done by a private consultant contracted by the sponsor

☐ Adaptation of global model/Canadian model done by an academic consultant contracted by the sponsor

☐ Other (please specify)

☐ Unclear

	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document	X		
Authors had independent control over the methods and right to publish analysis	X		

Appendix 4: Summary of Other Health Technology Assessment Reviews of Drug

Table 8: Other Health Technology Agency Findings

	NICE (April 2019)[31]
Treatment	SZC 5 g and 10 g sachets: • Correction: 10 g administered three times daily • Maintenance: starting dose of 5 g once daily, with titration to 10 g once daily or 5 g every other day.
Price	£7.12 (CAD$12.28) per 5 g sachet; £14.24 (CAD$24.57) per 10 g sachet.
Similarities with CDR submission	Patient-level simulation; modelled correction and maintenance treatment; restricted population to patients with CKD and/or HF; lifetime horizon
Differences with CDR submission	UK-specific health care use and costs; included only calcium polystyrene sulfonate as comparator; duration of correction treatment was 28 days
Sponsor's results[a]	**CKD** Emergency: SZC dominates Outpatient: £11,644 (CAD$20,135) per QALY (scenarios: £4,717 [CAD$8,157] to £19,815 [CAD$34,264]) **HF** Emergency: SZC dominates Outpatient: £18,158 (CAD$31,399) per QALY (scenarios: £13,602 [CAD$23,521] to £25,208 [CAD$43,590])
Issues noted by the review group	Maintenance treatment not given by NHS; trial patients had serum potassium levels lower than what is treated by NHS; trials did not reflect treatment of acute hyperkalemia; uncertain benefit in chronic hyperkalemia; insufficient evidence to prove that lowering serum potassium levels leads to improved outcomes
Results of reanalyses by the review group[a]	**CKD** Emergency: SZC dominates Outpatient: £17,179 (CAD$29,706) per QALY (scenarios: £39,287 [CAD$67,935]) **HF** Emergency: SZC dominates Outpatient: £24,291 (CAD$42,004) per QALY (scenarios: £19,385 [CAD$33,521] to £111,035 [CAD$192,002])
Recommendation[b]	SZC is recommended as an option for treating hyperkalemia in adults only if: • it needs treating in an emergency care setting • the drug is stopped after 28 days of maintenance treatment (or earlier if hyperkalemia resolves)

CDR = CADTH Common Drug Review; CKD = chronic kidney disease; HF = heart failure; NHS = National Health Services; NICE = National Institute for Health and Care Excellence; QALY = quality-adjusted life-year; SZC = sodium zirconium cyclosilicate.

Note: The currency conversion was performed using the average of 2019 monthly exchange rates from the Bank of Canada (£1 = CAD$1.73).[32]

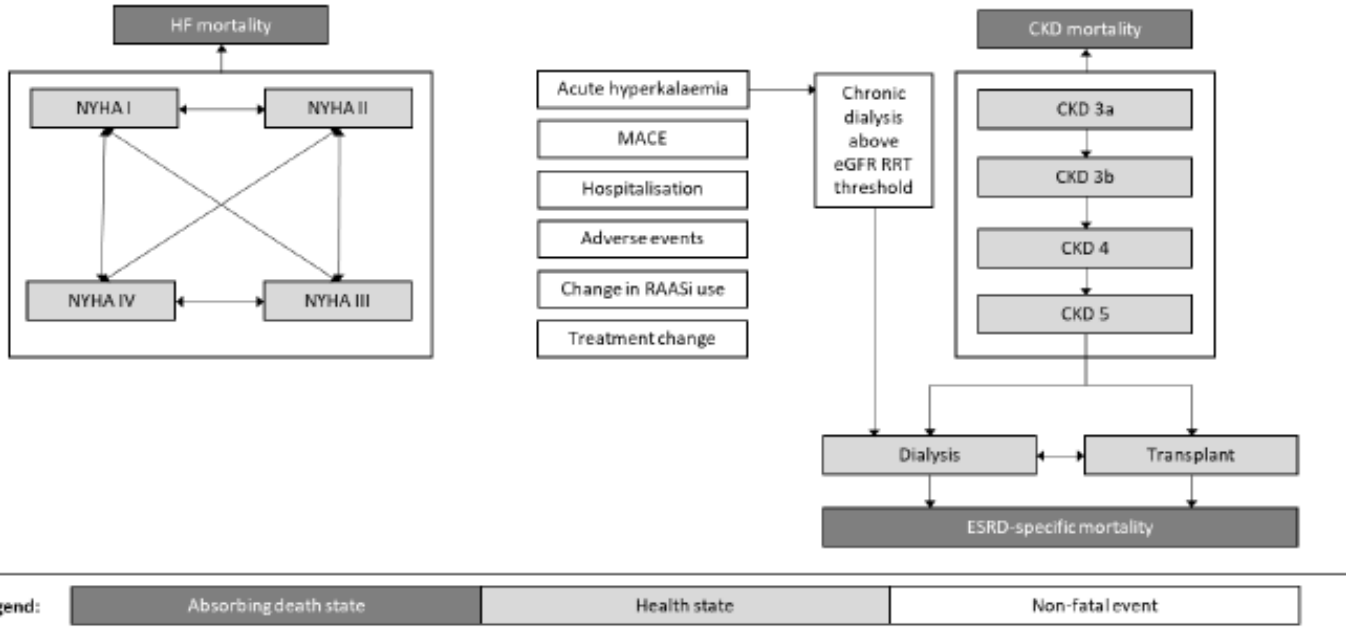
[a] Results based on revised base case from committee papers.[31]

[b] Recommendation based on findings from the appraisal consultation document.[31]

Appendix 5: Reviewer Worksheets

The patient-level model developed by the sponsor simulates the disease course of adult patients with hyperkalemia and an underlying condition of advanced CKD (non-dialysis CKD stage 3a to stage 5) and/or HF (NYHA functional class I, II, II, or IV). The sponsor's model structure is presented in Figure 1.

Figure 1: Sponsor's Model Structure

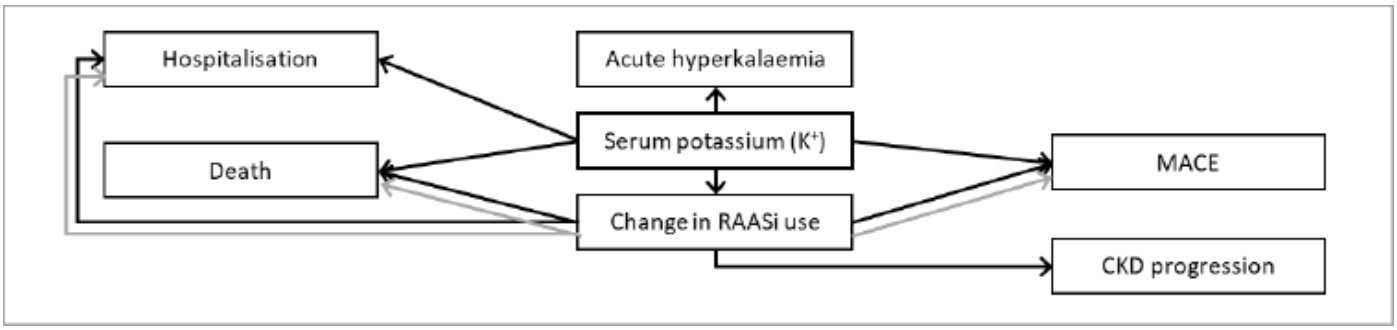


CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; HF = heart failure; NYHA = New York Heart Association; MACE = major adverse cardiac event; RAASi = renin-angiotensin-aldosterone system inhibitor; RRT = renal replacement therapy.

Source: Sponsor's submission.[2]

Relationships between serum potassium levels and events in CKD and HF populations are presented in Figure 2 and Figure 3, respectively. Grey arrows represent relationships that may be modelled according to level of RAASi use.

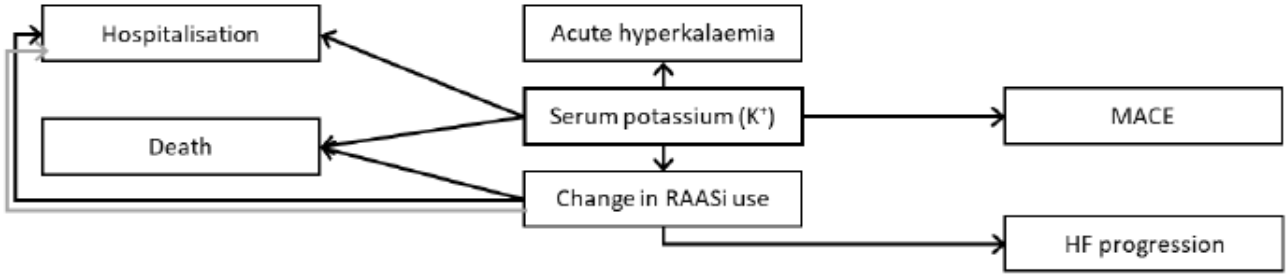
Figure 2: Modelled Relationships Between Potassium Levels and Outcomes in the Chronic Kidney Disease Population



CKD = chronic kidney disease; MACE = major adverse cardiac event; RAASi = renin-angiotensin-aldosterone system inhibitor.

Source: Sponsor's submission.[2]

Figure 3: Modelled Relationships Between Potassium Levels and Outcomes in the Heart Failure Population



HF = heart failure; MACE = major adverse cardiac event; RAASi = renin-angiotensin-aldosterone system inhibitor.

Source: Sponsor's submission[2]

Table 9: Sponsor's Data Sources

Data input	Description of data source	Comment
Baseline cohort characteristics	The baseline characteristics of the model population were based on the combined population of the sponsor-conducted studies ZS-004E and ZS-005.[10,11]	Acceptable. However, baseline characteristics of the overall population were inappropriately applied to subgroup analyses on HF-only and CKD-only populations.
Efficacy, safety, and withdrawals		
Efficacy	A mixed-effects regression model based on data from studies ZS-004 and ZS-005 was used to simulate treatment- and patient-specific S-K profiles.	The CADTH clinical review noted that the absence of comparisons between SZC and other potassium binders and treatments to reduce serum potassium levels makes it difficult to interpret the relative clinical benefit of the drug. Therefore, despite its demonstrated efficacy in reducing serum potassium levels, there is uncertainty as to the added clinical benefit of SZC. (See CADTH Clinical Review Report for further details.)
Adverse events	Adverse events reported included edema, worsening HT, GI effects (e.g., constipation, nausea) and hypokalemia. MACEs were dependent on S-K levels. Adverse event rates under BSC and SZC treatment were obtained from the published literature[16] and clinical trial data,[10] respectively.	Appropriate Appropriate
Discontinuation	Patients may discontinue SZC treatment due to RRT initiation if the duration of treatment reaches a defined limit (two days in the corrective phase, four cycles in the maintenance phase); if the S-K level falls outside an acceptable range (≥ 6.5 mmol/L or < 3.5 mmol/L); or for other reasons (lack of efficacy, adherence, AEs). The annual probability of SZC treatment	Appropriate

Data input	Description of data source	Comment
	discontinuation was estimated using data from the extended phase of Study ZS-005.[10] Only patients on BSC would discontinue or down-titrate RAASi treatment within the first 28 days of the model.	Inappropriate. The clinical experts consulted by CADTH noted that patients on SZC are also expected to discontinue RAASi treatment.
Natural history and mortality		
Natural history	Published literature was used to inform CKD and HF disease progression.[3,4]	Appropriate
Mortality	Mortality in the HF population was implemented using the Seattle Heart Failure Model.[12] Published literature was used to inform mortality in the CKD population.[33] If the general population probability of death exceeded the estimated probability of death based on comorbidity, RAASi use and S-K level, then the general population mortality was applied.	Inappropriate. Mortality rates were based on the study by Krogager et al. (2015),[5] which explored mortality risk of S-K levels in HF patients following myocardial infarction. Using mortality risk values based on a population that experienced a myocardial infarction was not appropriate, as more recent values are available for chronic HF patients.[6]
Utilities		
Health-state utilities	Health-state utilities for CKD, dialysis, transplant, HF and disutilities associated with MACE, hospitalization events, and dialysis complications were obtained from the literature.[7,17-20] Utility decrements for AEs were obtained from the literature.[21-23]	Inappropriate. Utilities for CKD stages were derived from the literature[7] from a time trade-off questionnaire. As per CADTH guidelines, utilities should be obtained from a generic classification system, such as the EQ-5D or Health Utilities Index. CADTH considered that the preference-based EQ-5D values derived from Jesky et al. (2016)[8] provided a more plausible set of utility values. Appropriate
Resource use and costs		
Drug	SZC cost was based on the sponsor's submitted price.[2] Treatment dosing was based on dose distributions from Study ZS-005.[10]	Appropriate Appropriate. However, alternative SZC dosing was explored in CADTH scenario analyses based on the product monograph.[1]
Adverse events	Renal replacement therapy and AE management costs were excluded from the model.	Appropriate
Health states	Health care costs were taken from the medical literature and official sources, such as provincial formularies and schedules of benefits. A micro-costing approach based on physician surveys was adopted to estimate the cost of several parameters.	Appropriate

AE = adverse event; BSC = best supportive care; CKD = chronic kidney disease; EQ-5D = EuroQol 5-Dimensions; GI = gastrointestinal; HF = heart failure; HT = hypertension; S-K = serum potassium; MACE = major adverse cardiac event; RAASi = renin-angiotensin-aldosterone system inhibitor; RRT = renal replacement therapy; SZC = sodium zirconium cyclosilicate.

Table 10: Sponsor's Key Assumptions

Assumption	Comment
Following RRT initiation, potassium profiles, treatment, and non-fatal events are no longer modelled. Only dialysis-related complications are allowed following RRT.	Acceptable due to the lack of efficacy and safety evidence on dialysis patients at the time of the submission. However, a recently published study evaluated SZC in dialysis patients and can be used as an efficacy data source for dialysis patients.[34]
BSC was assumed to consist of intermittent use of SPS or CPS for the correction of S-K as well as lifestyle interventions for the background maintenance of S-K.	Inappropriate. As per the clinical experts consulted by CDR, in clinical practice, patients would not receive SPS or CPS upon a hyperkalemia event. Instead, they would receive a diuretic and either discontinue RAASi or receive a reduced dose of RAASi to avoid future hyperkalemia events.
The sponsor assumed patients experiencing a hyperkalemia event would not incur a reduction in quality of life.	Appropriate. Disutilities related to MACE or hospitalization are included in the model. Since a hyperkalemia event will only generate disutilities through MACE or hospitalization, including a disutility for hyperkalemia would result in double counting.
AEs only incurred the cost of an additional consultation with a specialist.	Appropriate.
MACE, hospitalization, changes in RAASi use, and mortality were dependent on S-K levels.	Appropriate. However, the effect of change in RAASi use on S-K was not included in the model. This was considered inappropriate by the clinical experts.

AE = adverse event; BSC = best supportive care; CDR = CADTH Common Drug Review; CPS = calcium polystyrene sulfonate; S-K = serum potassium; MACE = major adverse cardiac event; RAASi = renin-angiotensin-aldosterone system inhibitor; RRT = renal replacement therapy; SPS = sodium polystyrene sulfonate; SZC = sodium zirconium cyclosilicate.

Table 11: Renin-Angiotensin-Aldosterone System Inhibitor Discontinuation and Down-Titration, by Potassium Category

S-K category (mmol/L)	Proportion of patients discontinuing (%)		Proportion of patients down-titrating (%)		Source
	Mean	SE	Mean	SE	
From maximum RAASi dose					
S-K < 5.1	0.000	0.000	0.000	0.000	Assumption[a]
S-K 5.1 to 5.4	0.244	0.003	0.178	0.002	Epstein et al. (2015)[14]
S-K ≥ 5.5	0.295	0.004	0.239	0.004	Epstein et al. (2015)[14]
From sub-maximum RAASi dose					
S-K < 5.1	0.000	0.000	NA	NA	Assumption[a]
S-K 5.1 to 5.4	0.282	0.002	NA	NA	Epstein et al. (2015)[14]
S-K ≥ 5.5	0.329	0.002	NA	NA	Epstein et al. (2015)[14]

S-K = serum potassium; NA = not applicable; RAASi = renin-angiotensin-aldosterone system inhibitor; SE = standard error.

[a] Changes in RAASi use reported by Epstein et al. following mild (S-K level 5.1 to 5.4) and moderate-to-severe (S-K level ≥ 5.0) hyperkalemia events; SEs estimated based on reported number of events.

Source: Sponsor's pharmacoeconomic submission.[2]

Table 12: Health State and Event Costs

Parameter	Mean ($)	SE	Source
Annual cost CKD stage 1 to 2	102.38	10.24	Micro-costing based on physician surveys
Annual cost CKD stage 3a	220.13	22.01	Micro-costing based on physician surveys
Annual cost CKD stage 3b	220.13	22.01	Micro-costing based on physician surveys
Annual cost CKD stage 4	394.70	39.47	Micro-costing based on physician surveys
Annual cost CKD stage 5 (pre-RRT)	5,592.60	559.26	Micro-costing based on physician surveys
Annual cost of dialysis	69,595.35	6,959.54	Beaudry et al. (2018)[35]
Dialysis access cost	621.35	62.14	MOHLTC Schedule of Benefits; physician services (R849)[36]
One-off cost of dialysis complications, weighted for type	0.00	0.00	Assumed included in annual cost of dialysis maintenance
One-off cost of transplant procedure, weighted for donor type	0.00	0.00	Assumed included in cost of organ transplant service
One-off organ transplant service cost	117,924.85	11,792.49	Barnieh et al. (2014)[37]
Annual cost of transplant maintenance	23,943.88	2,394.39	Barnieh et al. (2014)[37]
NYHA class I	1,379.13	137.91	Micro-costing based on physician surveys
NYHA class II	1,379.13	137.91	Micro-costing based on physician surveys
NYHA class III	3,684.19	368.42	Micro-costing based on physician surveys
NYHA class IV	7,086.53	708.65	Micro-costing based on physician surveys
Event cost: MACE	56,402.29	5,640.23	Cohen et al. (2014);[38] Mittman et al. (2012)[39]
Annual maintenance cost: MACE	4,764.01	476.40	Cohen et al. (2014)[38]
Event cost: hospitalization (CKD population)	8,487.00	848.70	CIHI: code CMG 480[40]
Event cost: hospitalization (HF population)	7,548.00	754.80	CIHI: code CMG 196[40]
Event cost: hospitalization (CKD + HF population)	8,487.00	848.70	Assumed equal to HF/CKD population
Event cost: RAASi discontinuation	263.40	26.34	Micro-costing based on physician surveys
Event cost: RAASi down-titration	395.10	39.51	Micro-costing based on physician surveys
Event cost: return to maximum RAASi use	275.40	27.54	User-defined on RAASi dose alteration sheet

CIHI = Canadian Institute for Health Information; CKD = chronic kidney disease; CMG = case mix group; HF = heart failure; MACE = major adverse cardiac event; MOHLTC = Ministry of Health and Long-Term Care; NYHA = New York Heart Association; RAASi = renin-angiotensin-aldosterone system inhibitor; RRT = renal replacement therapy; SE = standard error.

Source: Sponsor's pharmacoeconomic submission.[2]

Table 13: Costs Applied to Renin-Angiotensin-Aldosterone System Inhibitor Use

Parameter	CKD only ($)	HF only ($)	CKD + HF ($)	Source
Annual cost of RAASi: optimal therapy (max)	149.29	149.29	149.29	Micro-costing based on physician surveys
Annual cost of RAASi: suboptimal therapy (sub-max)	97.01	97.01	97.01	Micro-costing based on physician surveys

CKD = chronic kidney disease; HF = heart failure; RAASi = renin-angiotensin-aldosterone system inhibitor.

Source: Sponsor's pharmacoeconomic submission.[2]

If AEs are restricted to the correction phase of hyperkalemia, the average AE-related cost and disutility are applied at the incidence of acute hyperkalemia to reflect a three-day duration of active treatment. If AE disutilities and costs are applied over the duration of treatment, the average annual AE-related cost and disutility are applied to each cycle during which a patient remains on treatment. Therefore, disutilities were scaled to reflect the assumption that the impact of each AE would last 28 days within each year of treatment (i.e., 1/13 days).

Table 14: Model Inputs Associated With Disutility of Adverse Events

Treatment arm	SZC[a]	BSC[b]	Source
Edema (generalized and peripheral)	–0.0029	–0.0375	Assumed equal to hypertension
Worsening hypertension	–0.0029	–0.0375	Sullivan et al. (2011)[21]
Constipation	–0.0056	–0.0727	Sullivan et al. (2011)[21]
Diarrhea	–0.0008	–0.0100	Kristiansen et al. (1999)[22]
Nausea	–0.0037	–0.04802	Nafees et al. (2008)[23]
Hypomagnesemia	–0.0028	–0.0095	Sullivan et al. (2011)[21]
Anorexia	–0.0029	–0.0368	Sullivan et al. (2011)[21]
Hypokalemia	0.0000	0.0000	Assumption
Anemia	–0.0015	–0.0200	Sullivan et al. (2011)[21]
Urinary tract infection	–0.0004	–0.0054	Sullivan et al. (2011)[21]

BSC = best supportive care; SZC = sodium zirconium cyclosilicate.

[a] Applied throughout treatment (applied over duration of each cycle).

[b] Applied at correction of serum potassium only (applied for three days at each event).

Source: Sponsor's pharmacoeconomic submission.[2]

Sponsor's Base Case

Table 15: Sponsor's Base Case: Acute Correction Phase

	Total costs ($)	Incremental cost of SZC ($)	Total QALYs	Incremental QALYs of SZC	Incremental cost per QALY ($)
SZC	75,893	663	1.487	0.008	82,067
BSC	75,230	–	1.479	–	–

BSC = best supportive care; QALY = quality-adjusted life-year; SZC = sodium zirconium cyclosilicate.

Source: Sponsor's pharmacoeconomic submission.[2]

Table 16: Sponsor's Base Case: Maintenance of Normokalemia Phase

	Total costs ($)	Incremental cost of SZC ($)	Total QALYs	Incremental QALYs of SZC	Incremental cost per QALY ($)
SZC	89,965	28,719	1.481	0.343	83,693
BSC	61,246	–	1.138	–	–

BSC = best supportive care; QALY = quality-adjusted life-year; SZC = sodium zirconium cyclosilicate.
Source: Sponsor's pharmacoeconomic submission.[2]

Table 17: Detailed Costs From Sponsor's Base Case: Acute Correction

	SZC costs ($)	BSC costs ($)	Incremental costs ($)
Treatment	1,022	628	394
Adverse events	4	4	0
Acute HK	1,939	1,928	10
HF	7,534	7,497	38
CKD	2,114	2,113	1
MACE	42,756	42,583	173
Hospitalization	19,942	19,891	51
RAASi	582	586	–4
TOTAL	75,893	75,230	663

BSC = best supportive care; CKD = chronic kidney disease; HF = heart failure; HK= hyperkalemia; MACE = major adverse cardiac event; RAASi = renin-angiotensin-aldosterone system inhibitor; SZC = sodium zirconium cyclosilicate.
Source: Sponsor's pharmacoeconomic submission.[2]

Table 18: Detailed Costs From Sponsor's Base Case: Maintenance of Normokalemia

	SZC costs ($)	BSC costs ($)	Incremental costs ($)
Treatment	12,537	1,010	11,526
Adverse Events	155	6	148
Acute HK	3,293	5,520	2,227
HF	7,470	5,565	1,905
CKD	1,955	1,213	742
MACE	43,349	31,826	11,523
Hospitalization	20,609	15,566	5,043
RAASi	598	540	59
TOTAL	89,965	61,246	28,719

BSC = best supportive care; CKD = chronic kidney disease; HF = heart failure; HK= hyperkalemia; MACE = major adverse cardiac event; RAASi = renin-angiotensin-aldosterone system inhibitor; SZC = sodium zirconium cyclosilicate.
Source: Sponsor's pharmacoeconomic submission.[2]

Table 19: Summary of Predicted Clinical Outcomes of Sponsor's Base Case: Acute Correction

Cumulative events/patient	SZC	BSC	Incremental
Acute HK episodes	6.619	6.586	0.033
MACE	0.689	0.686	0.003
Hospitalization	2.452	2.446	0.007
RAASi discontinuation/down-titration	1.229	1.268	–0.040
Chronic dialysis prior eGFR threshold	0.000	0.000	0.000
Mortality	0.901	0.901	0.000

BSC = best supportive care; eGFR: estimated glomerular filtration rate; HK: hyperkalemia; MACE = major adverse cardiac event; RAASi: renin-angiotensin-aldosterone system inhibitor; SZC = sodium zirconium cyclosilicate.
Source: Sponsor's pharmacoeconomic submission.[2]

Table 20: Summary of Predicted Clinical Outcomes of Sponsor's Base Case: Maintenance of Normokalemia

Cumulative events/patient	SZC	BSC	Incremental
Acute HK episodes	7.773	11.244	–3.470
MACE	0.701	0.518	0.182
Hospitalization	2.526	1.895	0.631
RAASi discontinuation/down-titration	1.329	1.335	–0.006
Chronic dialysis prior eGFR threshold	0.000	0.000	0.000
Mortality	0.914	0.958	–0.044

BSC = best supportive care; eGFR: estimated glomerular filtration rate; HK: hyperkalemia; MACE = major adverse cardiac event; RAASi: renin-angiotensin-aldosterone system inhibitor; SZC = sodium zirconium cyclosilicate.

Source: Sponsor's pharmacoeconomic submission.[2]

CADTH Reanalysis

Base-Case Results

Table 21: CADTH Base Case: Acute Correction

	Total costs ($)	Incremental cost of SZC ($)	Total QALYs	Incremental QALYs of SZC	Incremental cost per QALY ($)
SZC	97,161	1,423	1.649	0.008	187,924
BSC (no treatment)	95,738	–	1.642	–	–

BSC = best supportive care; QALY = quality-adjusted life-year; SZC = sodium zirconium cyclosilicate.

Table 22: CADTH Base Case: Maintenance of Normokalemia

	Total costs ($)	Incremental cost of SZC ($)	Total QALYs	Incremental QALYs of SZC	Incremental cost per QALY ($)
SZC	116,065	24,204	1.655	0.228	106,137
BSC (no treatment)	91,861	–	1.427	–	–

BSC = best supportive care; QALY = quality-adjusted life-year; SZC = sodium zirconium cyclosilicate.

Price Reductions

Table 23: CADTH Reanalysis Price-Reduction Scenarios: Acute Correction

Incremental cost-utility ratios ($/QALY) of SZC vs. BSC		
Price	**Base-case analysis submitted by sponsor**	**CADTH base case**
Submitted	**82,067**	**187,924**
10% reduction	71,048	172,433
20% reduction	60,030	144,781
30% reduction	**49,011**	141,587
40% reduction	37,993	126,097
50% reduction	26,974	110,608

Incremental cost-utility ratios ($/QALY) of SZC vs. BSC		
Price	**Base-case analysis submitted by sponsor**	**CADTH base case**
60% reduction	15,956	95,118
70% reduction	4,938	79,629
80% reduction	Dominates	64,140
90% reduction	Dominates	**48,505**

BSC = best supportive care; QALY = quality-adjusted life-year; SZC = sodium zirconium cyclosilicate; vs. = versus.

Note: BSC consists of no treatment in the CADTH base case.

Table 24: CADTH Reanalysis Price-Reduction Scenarios: Maintenance of Normokalemia

Incremental cost-utility ratios ($/QALY) of SZC vs. BSC		
Price	**Base-case analysis submitted by sponsor**	**CADTH base case**
Submitted	**83,693**	**106,137**
10% reduction	80,048	99,285
20% reduction	76,403	92,432
30% reduction	72,758	85,580
40% reduction	69,113	78,728
50% reduction	65,468	71,876
60% reduction	61,823	65,023
70% reduction	58,177	58,171
80% reduction	54,532	**51,319**
90% reduction	**50,887**	44,467

BSC = best supportive care; QALY = quality-adjusted life-year; SZC = sodium zirconium cyclosilicate; vs. = versus.

Note: BSC consists of no treatment in the CADTH base case.

Since the CADTH base case uses lower mortality rates for the HF population, patients in the model live longer and accrue higher total SZC treatment costs. This modification, along with the exclusion of SPS costs, results in SZC costs accounting for a larger percentage of the total costs in CADTH's base case than in the sponsor's base case. Therefore, a lower price reduction is needed to achieve an ICER below $50,000 per QALY in the CADTH base case (approximately 85%) than in the sponsor's base case (approximately 90%).

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