5.19 SODIUM ZIRCONIUM CYCLOSILICATE, Sodium zirconium cyclosilicate hydrate 5 g powder for oral liquid, 30 sachets, Sodium zirconium cyclosilicate hydrate 10 g powder for oral liquid, 30 sachets, Lokelma®, ASTRAZENECA PTY LTD.

1 Purpose of submission

1.1 The Category 2 submission requested a General Schedule Authority Required (Telephone/Online) listing for sodium zirconium cyclosilicate (SZC) the treatment of chronic hyperkalaemia in patients with chronic kidney disease Stage 3-4.

1.2 Listing was requested on the basis of a cost-minimisation approach versus patiromer sorbitex calcium (patiromer).

Table 1: Key components of the clinical issue addressed in the submission

Component	Description
Population	Adult patients with CKD stage 3-4 with chronic hyperkalaemia (≥2 episodes of serum potassium ≥6.0 mmol/L in the previous 12 months), who are receiving ≥1 RAASi medicine or are indicated for an RAASi medicine but not able to tolerate this due to prior occurrence of hyperkalaemia.
Intervention	SZC starting at 5 g once daily, up titrated to a maximum dose of 10 g once daily if needed.
Comparator	Patiromer sorbitex calcium 8.4 g to 16.8 g daily (in twice daily split doses).
Outcomes	Maintenance of safe and acceptable serum potassium levels; reduction in recurrent/chronic episodes of hyperkalaemia; maintenance or optimisation of guideline recommended maximum RAASi doses.
Clinical claim	SZC is equivalent to patiromer in terms of efficacy (lowering serum potassium to the normal range and enabling patients to remain on guideline recommended RAASi doses), and similar to patiromer in terms of safety.

Source: Table 1-1, p15 of the submission.
Abbreviations: CKD, chronic kidney disease; RAASi, renin angiotensin aldosterone system inhibitor; SZC, sodium zirconium cyclosilicate.

2 Background

Registration status

2.1 Sodium zirconium cyclosilicate (5 g and 10 g sachets) was submitted under the TGA/PBAC parallel process. At the time of PBAC consideration, the ratified Advisory Committee on Medicines (ACM) outcome was available, with the ACM concluding SZC "to have an overall positive benefit-risk profile for the indication: treatment of hyperkalaemia in adult patients." This is consistent with the TGA indication for patiromer.

Previous PBAC consideration

2.2 SZC has not previously been considered by the PBAC.

2.3 At the March 2023 meeting, the PBAC recommended patiromer for the treatment of chronic hyperkalaemia in adults with chronic kidney disease (CKD) Stage 3-4 with chronic hyperkalaemia (≥2 episodes of serum potassium (K+) ≥6.0 mmol/L in the previous 12 months), who are receiving ≥1 RAASi medicine or are indicated for a RAASi medicine but not able to tolerate this due to prior occurrence of hyperkalaemia (Patiromer Public Summary Document (PSD), March 2023 PBAC meeting). Patiromer was listed on the PBS on 1 September 2023.

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Requested listing

3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty packs	Max. Qty units	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
SODIUM ZIRCONIUM CYCLOSILICATE					
Sodium zirconium cyclosilicate hydrate, 5 g powder for oral liquid, 30 sachets	1	30	5	Published: $[redacted] Effective: TBD	Lokelma AstraZeneca Pty Ltd
Sodium zirconium cyclosilicate hydrate, 10 g powder for oral liquid, 30 sachets	1	30	5	Published: $[redacted] Effective: TBD	Lokelma AstraZeneca Pty Ltd
Restriction Summary [new] / Treatment of Concept: [new]					
Category / Program: GENERAL – General Schedule (Code GE)					
Prescriber type: ☒ Medical Practitioners					
Restriction type: ☒ Authority Required (telephone/electronic via PBS Authorities system)					
Administrative advice: *Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333*					
Administrative advice: *Special pricing arrangements apply*					
Indication: Chronic hyperkalaemia					
Treatment Phase: Initial PBS subsidised treatment					
Population criteria:					
Patient must have stage 3 to stage 4 chronic kidney disease					
Clinical criteria:					
The condition must be inadequately controlled by a low potassium diet,					
AND					
Clinical criteria:					

Patient must have experienced at least 2 episodes of hyperkalaemia (defined as serum potassium levels of at least 6.0 mmol/L) within the 12 months prior to commencing this drug,
AND
Clinical criteria:
The treatment must not be in place of emergency treatment of hyperkalaemia.
AND
Clinical criteria:
Patient must be undergoing treatment with a renin angiotensin aldosterone system inhibitor; OR
Patient must be indicated for treatment with a renin angiotensin aldosterone system inhibitor; but ~~not able~~ unable to tolerate this due to prior occurrence of hyperkalaemia,
Treatment criteria:
Must be treated by a specialist medical practitioner *with experience in the diagnosis and management of chronic kidney disease.*

Restriction Summary [new] / Treatment of Concept: [new]
Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: ☒ Medical Practitioners
Prescriber type: ☒ Nurse practitioners
Restriction type: ☒ STREAMLINED
Administrative advice: *Special pricing arrangements apply*
Administrative advice: *Continuing Therapy Only:* *For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.*
Indication: Chronic hyperkalaemia
Treatment Phase: Continuing ~~PBS-subsidised~~ treatment
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition
AND
Clinical criteria:
The treatment must not be in place of emergency treatment of hyperkalaemia.
AND
Clinical criteria:
Patient must be undergoing treatment with a renin angiotensin aldosterone system inhibitor
Treatment criteria:
Patient must not be undergoing dialysis

3.2 The submission acknowledged that patiromer was listed on the PBS subject to a special pricing arrangement and that a similar arrangement would apply to SZC. The requested published price of SZC was based on a cost-minimisation approach compared to the published price of patiromer. As the effective price of patiromer was not known during the submission, the effective price of SZC was not estimated.

3.3 The draft SZC Product Information recommends SZC for the treatment of acute hyperkalaemia (correction phase) and chronic hyperkalaemia (maintenance phase). PBS listing of SZC for acute hyperkalaemia was not requested.

3.4 The requested restriction was narrower than the TGA indication as it limited PBS subsidised treatment to patients with moderate to severe hyperkalaemia (≥2 episodes of serum K+ ≥6.0 mmol/L in the prior 12 months), and CKD stage 3-4 treated with a RAASi medicine, uncontrolled by a low potassium diet. Continuing treatment with SZC will cease on progression to end-stage kidney disease (ESKD) treated with dialysis.

3.5 The requested restriction was also substantially narrower than the inclusion criteria of the key clinical trials (ZS004/004e, ZS005), which only required one confirmed episode hyperkalaemia (serum K+ ≥ 5.1 mmol/L) and did not include criteria related to CKD or the use of RAASi medicines.

3.6 The restriction was generally consistent with the PBS restriction for patiromer.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 Hyperkalaemia is a common electrolyte abnormality resulting from a variety of causes related to decreased potassium excretion, transcellular potassium shifts or exogenous sources, and may be exacerbated by administration of medicines impacting potassium excretion via the kidney; e.g. RAASi, nonsteroidal anti-inflammatory drugs (NSAIDs), and potassium sparing diuretics (spironolactone). Hyperkalaemia is most commonly observed in patients with acute kidney injury (AKI) and/or CKD, particularly in combination with type 2 diabetes mellitus (T2DM) and/or chronic heart failure (CHF), and if treated with RAASi therapies (Palmer et al., 2021).

4.2 A diagnosis of hyperkalaemia is based on laboratory assessed serum potassium concentrations and sometimes supported by clinical features (muscle weakness, ascending paralysis, cardiac conduction abnormalities, arrhythmias and other electrocardiograph (ECG) changes). Untreated, hyperkalaemia may result in paralysis of the respiratory muscles, fatal cardiac arrhythmias and sudden death.

4.3 Hyperkalaemia in CKD may be managed by diet control. However, the efficacy of diet is heterogenous (Joshi et al., 2023), compliance is difficult (Hu et al., 2021) and may conflict with other diet managed conditions (e.g. heart smart diet; Kalantar-Zadeh et al., 2015). Potassium binders offer an additional treatment option for the management of hyperkalaemia.

4.4 SZC is a non-absorbed, non-polymer, inorganic powder with a uniform micropore structure that preferentially captures potassium in exchange for hydrogen and sodium cations. SZC captures potassium in the gastrointestinal tract, reducing serum absorption of free potassium, and increasing faecal potassium excretion (Packham et al., 2015).

4.5 The submission positioned SZC as an alternative to patiromer in the treatment of hyperkalaemia in patients with CKD stage 3-4 not adequately controlled with dietary counselling and introduction of a low potassium diet, after initial short term treatment with SPS/CPS resins and at least 2 episodes of hyperkalaemia with a serum potassium ≥ 6.0 mmol/L.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 The submission nominated patiromer as the main comparator. The main argument provided in support of this nomination was that patiromer is an alternative selective potassium binder with the same place in therapy listed on the PBS. The ESC considered that patiromer was the appropriate comparator.

5.2 The submission claimed that calcium polystyrene sulfonate (CPS) and sodium polystyrene sulfonate (SPS) binders were not appropriate comparators, as these agents are not recommended for long term use, have poor tolerability, unselective modes of action, unpredictable potassium lowering outcomes, are associated with severe gastrointestinal adverse events (Rossignol and Pitt 2023), and are not listed on the PBS for the treatment of chronic hyperkalaemia.

5.3 Given patiromer was recommended for listing on the PBS for chronic hyperkalaemia at the March 2023 PBAC meeting, on a cost minimisation basis versus CPS/SPS, these treatments may be appropriate secondary comparators.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor provided a clinician statement for this item. The clinician stated that there was strong evidence that hyperkalaemia results in down titration or cessation of RAASi, in turn increasing cardiorenal events and mortality. The treatment of hyperkalaemia with SZC can allow patients with CKD or heart failure to maintain optimal RAASi therapy and reduce the progression to Stage 5 CKD or the initiation of dialysis.

Consumer comments

6.2 The PBAC noted and welcomed the input from an individual, health care professionals (2), a medical organisation and a consumer group via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with SZC, including allowing individuals to (i) continue beneficial therapies such as RAASis (which slow the progression of CKD and heart failure), (ii) maintain a healthy diet while undergoing treatment, and (iii) delay the initiation of dialysis. A choice of treatment options was also cited as a benefit with different patient populations being better

suited to SZC or patiromer.

6.3 Kidney Health Australia noted that CKD is most prevalent in the most disadvantaged Australians, and that individualised dietary intervention via a specialised renal dietitian is not available/possible for many individuals. As such, they note that SZC provides an additional treatment option that is readily accessible to all patients. The need for access to alternative treatment options was also a concern with recent interruptions to the supply of patiromer noted.

6.4 The PBAC noted the advice received from the Australia and New Zealand Society of Nephrology (ANZSN) clarifying the likely use of SZC in clinical practice. The PBAC specifically noted the advice that although the use of SZC would require ongoing monitoring of blood potassium levels, this was already standard practice for the management of patients with moderate to severe CKD. The PBAC further noted that the ANZSN strongly supported the submission. The PBAC noted that this advice was supportive of the evidence provided in the submission.

Clinical trials

6.5 The submission was based on:

- One SZC trial with (i) a single-arm, open-label acute phase and (ii) a randomised, double-blind, placebo-controlled maintenance/withdrawal phase (ZS004), and its associated open label extension study (ZS004e).
- One single arm, open label, long term, SZC study (ZS005).
- One patiromer trial with (i) a single-arm, open-label initial treatment phase (OPAL-HK Part A) and (ii) a randomised, single-blind, placebo-controlled maintenance/withdrawal phase (OPAL-HK Part B).
- One randomised, dose-finding patiromer trial (AMETHYST DN).

6.6 The patiromer studies were previously considered by the PBAC at the March 2023 meeting (Patiromer PSD, March 2023 PBAC meeting).

6.7 No head-to-head trials comparing SZC with patiromer were identified. In addition to the whole of trial results of ZS004, ZS004e and ZS005, the submission presented the following analyses:

- An anchored matching-adjusted indirect comparison (MAIC) of SZC versus patiromer, in the chronic hyperkalaemia setting (maintenance/withdrawal phase), with placebo as the common reference, based on the ZS004 and OPAL-HK trials.
- An unanchored MAIC based on the ZS004, ZS005 and OPAL-HK trials, assuming a proxy placebo common reference, as sensitivity analysis.
- An unanchored MAIC of SZC versus patiromer in the acute hyperkalaemia setting (acute phase), based on the ZS004 and OPAL-HK trials, as supporting evidence.

6.8 Details of the trials presented in the submission are provided in Table 2.

Table 2: Trials presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Indirect randomised trials		
SZC versus placebo		
ZS004 HARMONIZE (NCT 02875834)	A phase 3 multicenter, multi-phase, multi-dose, prospective, randomised double-blind, placebo-controlled maintenance study to investigate the safety and efficacy of sodium zirconium cyclosilicate, an oral sorbent, in subjects with hyperkalaemia.	Clinical Study Report 3 December 2014
	Kosiborod M., Rasmussen H.S., Lavin P., et al. Effect of sodium zirconium cyclosilicate on potassium lowering for 28 days among outpatients with hyperkalaemia: the HARMONIZE randomised clinical trial.	Journal of the American Medical Association 2014; 312(21): 2223 - 2233.
	Peacock W., Rafique Z., Rasmussen H., et al. Sodium zirconium cyclosilicate (ZS-9) for severe hyperkalaemia: a post hoc analysis of the phase 3 HARMONIZE trial.	Academic Emergency Medicine 2015; 22(5): S69.
	Packham D., Rasmussen H., Lavin P., et al. Maintenance of normal serum potassium with sodium zirconium cyclosilicate (ZS-9) in subgroup of patients with history of chronic kidney disease and on RAASi from the phase 3 randomised, double-blind, placebo-controlled HARMONIZE study.	Nephrology Dialysis Transplantation 2015; 30: iii69.
	Levy P., Rasmussen H.S., Lavin P.T., et al. Sodium zirconium cyclosilicate for patients with severe hyperkalaemia: Subgroup analysis of the phase 3, international, multicentre, randomised, double-blind, placebo-controlled HARMONIZE trial.	Annals of Emergency Medicine 2015; 66(4): S93.
ZS004e (NCT021070920)	An open-label extension to study ZS004, a phase 3 multicentre, multi-phase, multi-dose, prospective, randomised, double-blind, placebo-controlled maintenance study to investigate the safety and efficacy of sodium zirconium cyclosilicate), an oral sorbent, in subjects with hyperkalaemia.	Clinical Study Report 14 September 2015.
	Roger S.D., Spinowitz B.S., Lerma E.V., et al. Efficacy and safety of sodium zirconium cyclosilicate for treatment of hyperkalaemia: An 11-month open-label extension of HARMONIZE.	American Journal of Nephrology 3 December 2019; 50(6): 473-480.
ZS005 (NCT02163499)	A phase 3 multicentre, multi-dose, open-label maintenance study to investigate the long-term safety and efficacy of ZS (sodium zirconium silicate), an oral sorbent, in subjects with hyperkalaemia.	Clinical Study Report 23 April 2014.
	Roger, S.D., Lavin P.T., Lerma E.V., et al. Long-term safety and efficacy of sodium zirconium cyclosilicate for hyperkalaemia in patients with mild/moderate versus severe/end-stage chronic kidney disease: comparative results from an open-label, Phase 3 study.	Nephrology Dialysis Transplantation 2021; 36(1): 137-150.
Patiromer versus placebo		
OPAL-HK (NCT01810939)	Weir M.R., et al. Patiromer in patients with kidney disease and hyperkalaemia receiving RAAS inhibitors.	New England Journal of Medicine 2015; 372(3): 211-221.
AMETHYST DN (NCT01371747)	Bakris G.L., Pitt B., Weir M.R. et al. Effect of patiromer on serum potassium level in patients with hyperkalemia and diabetic kidney disease: the AMETHYST-DN randomized clinical trial.	Journal of the American Medical Association 2015; 314(2):151-161.
	Pitt B., Bakris G.L., Weir M.R., et al. Long-term effects of patiromer for hyperkalaemia treatment in patients with mild heart failure and diabetic nephropathy on angiotensin-converting enzymes/angiotensin receptor blockers: results from AMETHYST DN.	European Society of Cardiology: Heart Failure 2018; 5(4): 592-602.

Source: Table 2-2, pp34-35 of the submission.

6.9 The key features of the trials included in the submission are summarised in Table 3.

Table 3: Key features of the trials included in the submission

Trial	N	Design/duration	Risk of bias	Patient population	Key outcomes
SZC versus placebo					
ZS004	258	Phase 3, MC Acute phase: SA, OL up to 48 hours	High	Adults ≥18 years; i-STAT K+ ≥5.1 mmol/L	- Mean change in serum K+ from Acute Phase base line - % of patients achieving serum K+ < 5.1 mmol/L at 24 and 48 hours
	237	Phase 3, MC Maintenance/withdrawal phase: R, DB, PC 28 days	Low	Completed Acute Phase with i-STAT K+ 3.5 to 5.0 mmol/L	- LS mean of all K+ values, - % of patients with serum K+ < 5.1 mmol/L, - Safety
ZS004e	121	ZS004 extension, MC Acute phase*: SA, OL up to 48 hours Maintenance phase: SA, OL 336 days	High	Completed study ZS004 with i-STAT K+ 3.5 to 6.2 mmol/L	- % of patients with serum K+ < 5.1 mmol/L or <5.5 mmol/L, - Safety
ZS005	751	Phase 3, MC Acute phase: SA, OL up to 72 hours Maintenance phase: SA, OL 365 days	High	Adults ≥18 years; i-STAT K+ ≥5.1 mmol/L	- % of patients with serum K+ < 5.1 mmol/L, - Safety
Patiromer versus placebo					
OPAL-HK Part A	243	Phase 3, MC Initial treatment phase: SA, SB 4 weeks	High	Adults 18-80 years; CKD Stage 3-4; K+ 5.1 to < 6.5 mmol/L; ≥1 RAASi therapy	- Mean change in K+ from baseline to wk 4, - % of patients achieving K+ thresholds, - Safety
OPAL-HK Part B	104	Phase 3, MC Maintenance/withdrawal phase: R, SB, PB 8 weeks	High	Completed OPAL-HK Part A with K+ 3.8 to < 5.1 mmol/L; Part A baseline K+ ≥ 5.5 mmol/L; ≥1 RAASi at Part A week 4	- Mean change in K+ from baseline to wk 8, - % of patients with K+ ≥5.5 mmol/L, - Safety
AMETHYST-DN	306	Phase 2, MC, R, OL 52 weeks	High	Adults 30-80 years; CKD Stage 3-4; K+ 5.0 to <6.0 mmol/L; T2DM diagnosed at 30+ years on pharmacological intervention; hypertension; ≥1 RAASi	- Mean change in K+ baseline to wks 4 & 8, or dose titration, - % of patient achieving K+ thresholds, - Safety

Source: Sections 2.3-2.4, pp36-75 of the submission.

Abbreviations: CKD, chronic kidney disease; DB, double blind; K+, potassium; MC, multi-centre; PC, placebo controlled; OL, open label; R, randomised; RAASi, renin angiotensin aldosterone system inhibitor; SA, single arm; SB, single blind; SZC, sodium zirconium cyclosilicate; T2DM, type 2 diabetes mellitus.

* Two subjects only

6.10 The acute treatment phases of ZS004, ZS004e and ZS005 SZC trials, and longer-term extended dosing phases of the ZS004e and ZS005 SZC trials were open label, single arm studies with a high risk of bias. The ZS004 maintenance/withdrawal phase was a randomised, double-blind, placebo-controlled trial with a low risk of bias.

6.11 The PBAC previously noted that the risk of bias in the patiromer OPAL-HK and AMETHYST-DN trials was high, given the lack of randomisation in OPAL-HK Part A and potential unblinding in OPAL-HK Part B, and the lack of control arm in the AMETHYST-DN trial (paragraph 6.8, Patiromer PSD, November 2020 PBAC meeting; paragraphs 6.9, 6.18-6.19, 7.5, Patiromer PSD, November 2022 PBAC meeting).

6.12 In the SZC trials (ZS004, ZS004e, ZS005), potassium samples were analysed by i-STAT (a hand-held cartridge device) and a central laboratory. Eligibility, SZC dose titration and treatment decisions were based on the i-STAT potassium values (available on site), while all statistical analyses were conducted using central laboratory serum potassium values. The submission acknowledged that potassium values measured by i-STAT were on average 0.15 mmol/L lower than central laboratory serum potassium values.

6.13 The objectives of the SZC studies were related to achieving and maintaining normokalaemia. The objectives of the patiromer trials were related to achieving and maintaining normokalaemia while also maintaining optimal RAASi therapy. This resulted in substantial differences in study design, with study drug dose titration and participant flow in the SZC ZS004, ZS004e and ZS005 studies based on i-STAT potassium values, and in the patiromer OPAL-HK and AMETHYST-DN trials based on serum potassium and RAASi therapy optimisation. The ESC, noting that the SZC studies did not provide any substantial evidence that maintaining normokalaemia allowed patients to maintain optimal RAASi therapy, considered that the PBAC would need to determine if maintenance of normokalaemia was an appropriate surrogate outcome for RAASi use. The pre-PBAC response highlighted that ZS005 included assessment of RAASi use as exploratory endpoints and, that like the SZC trials, the patiromer trials also used reduction of potassium as their primary endpoint.

6.14 The SZC ZS004, ZS004e and ZS005 studies included adults with one episode of hyperkalaemia. This resulted in a substantially broader population compared to the patiromer OPAL-HK and AMETHYST-DN trials, which included adults with hyperkalaemia and CKD stage 3-4, stabilised on RAASi medicines. Consequently, there were substantial differences in the populations included in the SZC and patiromer trials in terms of CKD, RAASi medicine use and comorbidities (T2DM, heart failure and hypertension).

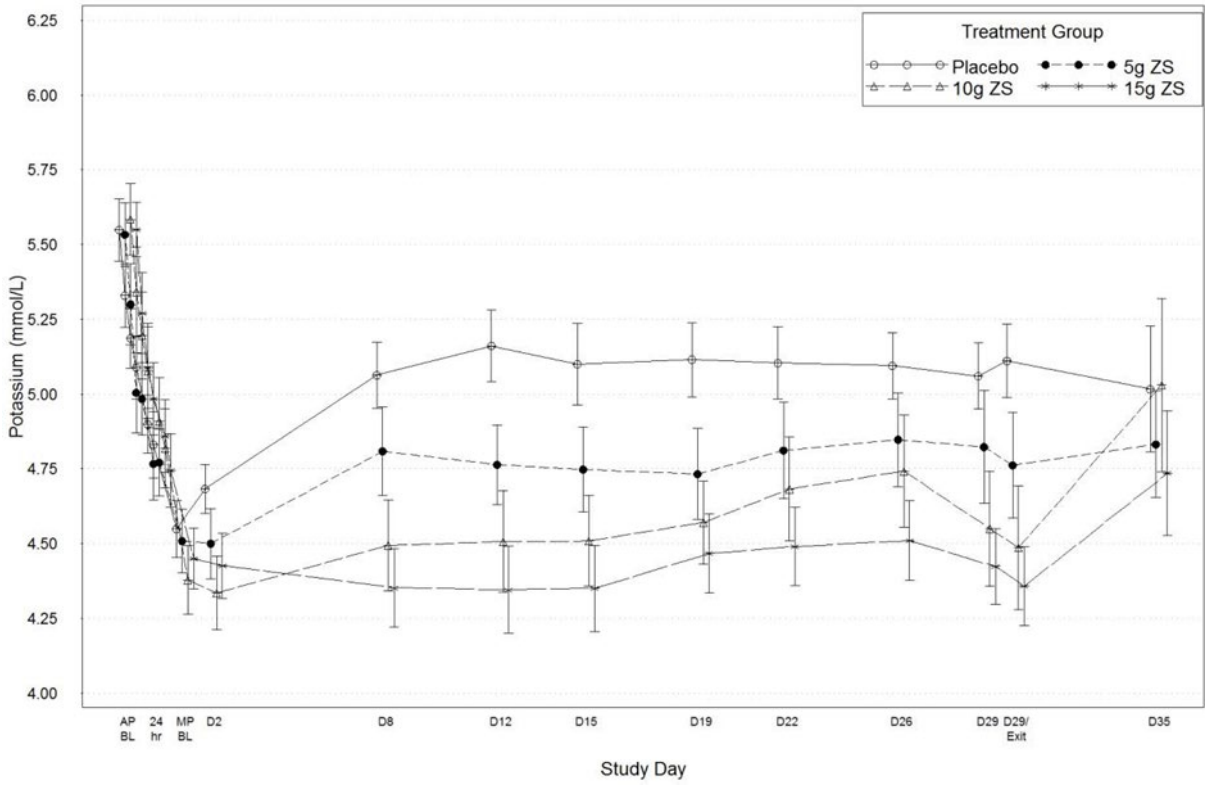
6.15 Consistent with the broad inclusion criteria, patient demographic and disease characteristics in the SZC clinical studies were substantially different to the eligible Australian population in terms of chronicity of hyperkalaemia, definition of hyperkalaemia requiring pharmacological intervention, age, and comorbid CKD, heart failure and diabetes. The SZC clinical studies included patients with mild to severe hyperkalaemia, regardless of hyperkalaemia episodicity, CKD status, and RAASi use, and may not reflect the eligible Australian population. The pre-PBAC response stated that the SZC trials included patients with disease characteristics that aligned with the requested PBS restriction. Further, the pre-PBAC response noted that the results for various subgroups of interest (including CKD, eGFR < 60 mL/min, use of RAASi and S-K

≥ 6.0 mmol/L) aligned with the overall trial results, suggesting that the trial results are applicable to the Australian requested population.

Comparative effectiveness

6.16 Figure 1 summarises the ZS004 study mean serum potassium over time, from the Acute Phase baseline to the maintenance/withdrawal phase (herein referred to as the Maintenance Phase) Days 8 to 29 and end-of-study visits, in the ITT population.

Figure 1: ZS004 Acute Phase & Maintenance Phase: Mean serum potassium over time (ITT)



Source: Figure 2-3, p77 of the submission.
Abbreviations: AP, Acute Phase; BL, baseline; D, study day; ITT, intent-to-treat; MP, Maintenance Phase; ZS, sodium zirconium cyclosilicate.
Note: Vertical bars represent ± 2 standard errors.

6.17 Results of the ZS004 mean serum potassium over time showed a rapid decrease in serum potassium in all patients treated with SZC 10 g 3 times daily during the Acute Phase, and maintenance of lower serum potassium over time to end-of-study during the Maintenance Phase. Patients treated with SZC showed significantly lower serum potassium values compared to placebo from Day 8 to Day 29 (study exit), with lower mean serum potassium values associated with higher doses of SZC.

6.18 Table 4 summarises the proportions of patients maintaining normokalaemia during the Maintenance Phase of trial ZS004.

Table 4: ZS004 Maintenance Phase: proportions of patients remaining normokalaemic Days 8-29/EOS (ITT)

	SZC 5 g daily n/N (%)	SZC 10 g daily n/N (%)	SZC 15 g daily n/N (%)	Placebo n/N (%)
N	45	50	54	82
Baseline	42/45 (93.3%)	46/50 (92.0%)	50/54 (92.6%)	71/82 (86.6%)
Day 8	32/45 (71.1%)*	41/50 (82.0%)*	46/54 (85.2%)*	39/81 (48.1%)
Day 12	33/44 (75.0%)*	37/47 (78.7%)*	45/53 (84.9%)*	32/80 (40.0%)
Day 15	31/44 (70.5%)*	40/47 (85.1%)*	43/52 (82.7%)*	35/80 (43.8%)
Day 19	32/43 (74.4%)*	37/47 (78.7%)*	45/51 (88.2%)*	35/78 (44.9%)
Day 22	29/43 (67.4%)*	30/45 (66.7%)*	45/51 (88.2%)*	34/77 (44.2%)
Day 26	31/42 (73.8%)*	32/45 (71.1%)*	43/51 (84.3%)*	36/74 (48.6%)
Day 29	26/39 (66.7%)	31/38 (81.6%)*	39/43 (90.7%)*	37/73 (50.7%)
Day 29 (exit)	32/45 (71.1%)*	38/50 (76.0%)*	46/54 (85.2%)*	39/82 (47.6%)
Day 35 (EOS)	14/22 (63.6%)	13/27 (48.1%) *	14/20 (70.0%)*	16/31 (51.6%)

Source: Table 2-13, p81 of the submission.
Abbreviations: EOS, end-of-study; ITT, intent-to-treat; SZC, sodium zirconium cyclosilicate.
* Statistically significant compared to placebo (Fisher's exact test).
Note: Exit was last visit of extended Dosing Phase within 1 day of last dose of SZC. EOS included all patients with data within 7 (±1) days of the last dose of SZC.

6.19 Statistically significantly larger proportions of patients treated with SZC reported serum potassium values < 5.1 mmol/L at study visits, compared to placebo, with larger proportions reporting serum potassium values <5.1 mmol/L, associated with higher doses of SZC.

6.20 Results of mean serum potassium over time for the ZS004e and ZS005 Maintenance Phases show a rapid initial reduction in serum potassium to normokalaemia within 24-72 hours. Mean serum potassium remained normokalaemic in both trials up to 337-365 days, with evidence of rebound increases in serum potassium at end-of-study and during follow-up.

6.21 Overall, the results of the ZS004, ZS004e and ZS005 trials demonstrated that SZC was effective in the rapid reduction of serum potassium in patients with hyperkalaemia, and the maintenance of normokalaemia in these patients over a duration of treatment of up to 365 days.

Matching-adjusted indirect comparison (MAIC)

6.22 The submission acknowledged that an indirect comparison between the SZC studies and the patiromer trials was not appropriate given the substantial differences between in terms of study design (study drug titration protocols, study duration, serum potassium thresholds) and population demographic and disease characteristics (chronicity of hyperkalaemia, definition of hyperkalaemia requiring pharmacological intervention, and comorbid CKD, heart failure and diabetes). Therefore, the submission presented MAICs based on patient level data from patients treated with SZC in the ZS004 trial, weighted to reflect the baseline characteristics of the patients treated with patiromer in the OPAL-HK trial.

6.23 For the key Maintenance Phase MAIC analysis, anchored with a placebo common reference, treatment effect modifiers were selected by clinical judgement based on covariates adjusted for in the ZS004 primary outcome (age, study entry serum K+,

maintenance phase entry serum K+, CKD, T2DM, HF, and RAASi use). Estimates of patient-level outcomes based on weighted observations for patients receiving SZC were compared to reported estimates for patients receiving patiromer.

6.24 The submission suggested that although the ZS005 study did not contain a placebo arm, it had a similar design to ZS004 and it was reasonable to assume that the ZS004 placebo arm could be used as a relevant control arm for the ZS005 population. Therefore, the submission presented an anchored MAIC based on pooled individual patient data from the ZS004 and ZS005 studies, as a sensitivity analysis. Notwithstanding the similarities between study populations, the pooling of the ZS004 and ZS005 treatment arms in a comparison with the ZS004 placebo arm was not adequately justified but may be informative as a sensitivity analysis.

6.25 Serum potassium values on Day 28 of the Maintenance Phase were reported in ZS004, ZS005 and OPAL-HK Part B, and were used for the Maintenance Phase analyses. The SZC Day 28 mean potassium values were derived from the ZS004 and ZS005 individual patient data, and for patiromer were derived from OPAL-HK reported by Weir et al. (2015).

6.26 Table 5 presents the results of the SZC (ZS004) and patiromer (OPAL-HK) Maintenance Phase MAIC for mean difference in mean serum potassium at Day 29. The results for the sensitivity analysis pooling studies ZS004 and ZS005 were identical to the results for ZS004. This may have been a transcription error in the submission (see shaded cells below).

Table 5: Anchored MAIC Maintenance Phase: Mean difference in mean serum potassium between SZC (ZS004 and ZS005) and patiromer (OPAL-HK)

	ESS	SZC K+ mmol/L (95% CI)	Placebo K+ mmol/L (95% CI)	Patiromer[b] K+ mmol/L (95% CI)	Placebo K+ mmol/L (95% CI)	Mean difference (95% CI)
ZS004 versus OPAL-HK Observed						
SZC 5 g daily	150[a]	4.82 (4.63, 5.01)	5.06 (4.95, 5.17)	4.55 (4.43, 4.67)	4.95 (4.81, 5.09)	0.16 (-0.12, 0.45)
SZC 10 g daily		4.55 (4.36, 4.74)				-0.11 (-0.39, 0.17)
MAIC Maintenance set 1 (base case)						
SZC 5 g daily	42.18	5.02 (4.72, 5.32)	5.17 (4.96, 5.37)	4.55 (4.43, 4.67)	4.95 (4.81, 5.09)	0.26 (-0.18, 0.69)
SZC 10 g daily		4.71 (4.47, 4.95)				-0.06 (-0.41, 0.30)
MAIC Maintenance set 2						
SZC 5 g daily	24.21	4.87 (4.32, 5.42)	5.08 (4.83, 5.32)	4.55 (4.43, 4.67)	4.95 (4.81, 5.09)	0.19 (-0.66, 1.04)
SZC 10 g daily		4.71 (4.38, 5.05)				0.03 (-0.47, 0.54)
MAIC Maintenance set 3						
SZC 5 g daily	24.36	4.79 (4.41, 5.18)	5.03 (4.76, 5.30)	4.55 (4.43, 4.67)	4.95 (4.81, 5.09)	0.17 (-0.44, 0.78)
SZC 10 g daily		4.62 (4.35, 4.89)				-0.01 (-0.41, 0.39)
MAIC Maintenance set 4						
SZC 5 g daily	25.08	4.81 (4.48, 5.16)	5.19 (4.93, 5.45)	4.55 (4.43, 4.67)	4.95 (4.81, 5.09)	0.03 (-0.48, 0.53)
SZC 10 g daily		4.74 (4.44, 5.04)				-0.05 (-0.48, 0.38)
MAIC Maintenance set 5						
SZC 5 g daily	68.95	4.90 (4.69, 5.11)	5.22 (5.06, 5.37)	4.55 (4.43, 4.67)	4.95 (4.81, 5.09)	0.08 (-0.25, 0.41)
SZC 10 g daily		4.57 (4.32, 4.82)				-0.25 (-0.58, 0.08)
ZS004 and ZS005 (pooled) versus OPAL-HK (sensitivity analysis)[c] Observed						
SZC 5 g daily	927[a]	4.82 (4.63, 5.01)	5.06 (4.95, 5.17)	4.55 (4.43, 4.67)	4.95 (4.81, 5.09)	0.16 (-0.12, 0.45)
SZC 10 g daily		4.55 (4.36, 4.74)				-0.11 (-0.39, 0.17)
SZC pooled		4.76 (4.72, 4.80)				0.10 (-0.11, 0.31)
MAIC Maintenance set 1						
SZC 5 g daily	109.9	4.96 (4.61, 5.32)	5.10 (4.80, 5.39)	4.55 (4.43, 4.67)	4.95 (4.81, 5.09)	0.26 (-0.18, 0.69)
SZC 10 g daily		4.62 (4.33, 4.91)				-0.06 (-0.41, 0.30)
SZC pooled		4.72 (4.61, 4.83)				0.02 (-0.35, 0.40)

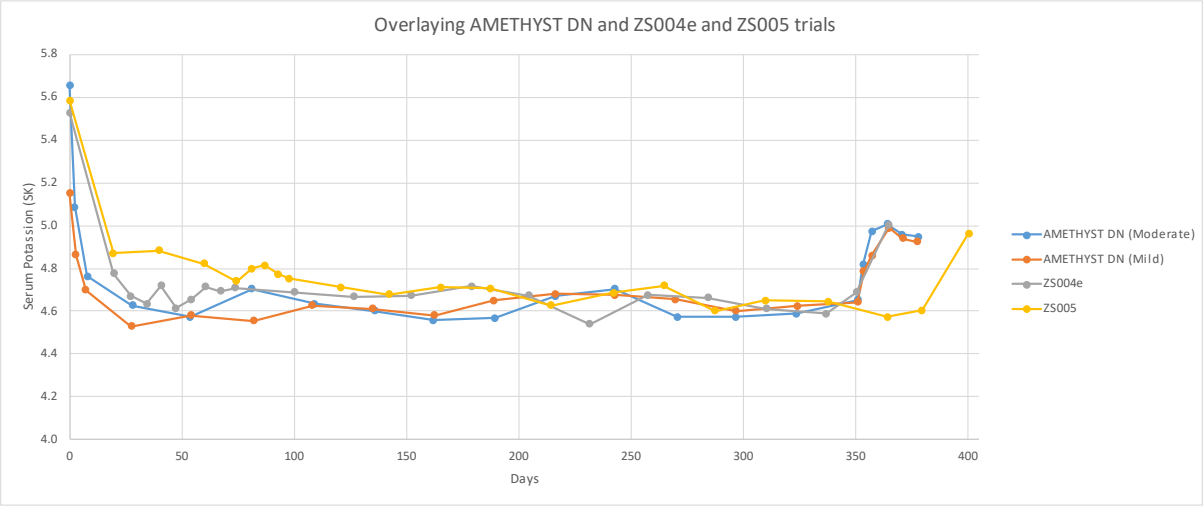
Source: Tables 12 and 13, p9 of the LOKELMA and Veltassa ITC Report_FIN April 2018, Attachment 2.2 of the submission.
Abbreviations: CI, confidence interval; ESS, effective sample size; SZC, sodium zirconium cyclosilicate.
[a] Effective sample size appears to include all patients treated with SZC in the ZS004 Maintenance Phase, including patients receiving the 15 g SZC dose strength, claimed to be excluded.
[b] Patiromer administered daily doses of 8.4 g (4.2 g 2 times daily) or 16.8 g (8.4 g 2 times daily).
[c] Anchored MAIC, assuming ZS004 placebo arm was a relevant control arm for the ZS005 population.
Note: Results shaded blue in the observed pooled ZS004 and ZS005 population appear to be identical to the results for the smaller ZS004 population and may be a transcription error in the submission. It is unclear if the SZC pooled treatment arms include ZS005 data.
Note that the results presented in Table 5are derived from post-hoc analyses conducted by the applicant during the evaluation by the PBAC specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for Study ZS004, ZS004e or ZS005. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose

6.27 Results of the Maintenance Phase anchored MAIC showed that patients treated with SZC 5 g and 10 g once daily, reported similar mean serum potassium values compared to patiromer after 29 days of treatment in the observed whole of trial and MAIC analyses. Serum potassium values were higher in the SZC and placebo patient data of the matched population, compared to the observed population. In addition, patients treated with SZC 10 g once daily reported lower serum potassium values compared to

the patients treated with SZC 5 g once daily. Similar results were observed in sensitivity analyses by alternative matching treatment modifiers (MAIC Maintenance sets 2-5).

6.28 The Pre-Sub-Committee Response (PSCR) presented a naïve comparison overlaying mean potassium concentration over time from the ZS004 and ZS005 SZC trials and the AMETHYST DN patiromer trial highlighting the comparability of mean serum potassium levels over time in patients receiving SZC and patiromer.

Figure 2: Overlay of mean serum potassium (mmol/L) over time in ZS004e, ZS005 and AMETHYST DN trials



Source: PSCR – Figure 1, page 3

6.29 Overall, the results of the MAIC analyses should be interpreted with caution for the following reasons:

- The selection of an anchored MAIC for the comparisons between the SZC and patiromer Maintenance Phase analyses may be appropriate, given the availability of a common reference (placebo) in each study. However, given the substantial differences between the ZS004 and OPAL-HK study designs in terms of study duration, study drug dose titration and study objectives, the assumption that these differences were adequately addressed by matching populations between studies, may not be reasonable.
- Matching of the selected treatment effect modifier variables in the MAIC Maintenance Phase analysis of the key outcome resulted in an effective sample size of 42.18 (down from 150 observed), suggesting poor overlap between the trial populations and substantial data loss associated with the MAIC methodology.
- It was unclear whether all relevant treatment effect variables were identified and matched in the analysis (e.g., eGFR < 60mL/min/1.73 m^2).

Comparative harms

6.30 Table 6 presents a summary of key treatment emergent adverse events in the ZS004 Maintenance Phase (Days 8 to 29), the ZS004e and ZS005 Maintenance Phases (Days 8 to 337/365), the OPAL-HK Part B (8 weeks) and AMETHYST-DN (52 weeks) trials.

Table 6: Summary of key treatment emergent adverse events in study maintenance phases (safety)

	ZS004				ZS004e	ZS005	OPAL-HK Part B		AMETHYST-DN
	SZC 5 g	SZC 10 g	SZC 15 g	Placebo	SZC	SZC	Patiromer	Placebo	Patiromer
N	45	51	56	85	123	746	55	52	304
Any AE	24 (53%)	15 (29%)	25 (45%)	27 (32%)	82 (67%)	489 (66%)	26 (47%)	26 (50%)	210 (69%)
Any related AE	3 (7%)	3 (6%)	6 (11%)	7 (8%)	14 (11%)	90 (12%)	NR	NR	61 (20%)
Any severe AE	4 (9%)	1 (2%)	3 (5%)	1 (1%)	20 (16%)	125 (17%)	NR	NR	NR
Deaths	0	1 (2%)	0	0	0	8 (1%)	0	1 (2%)	15 (5%)
Any serious AE	5 (11%)	2 (4%)	3 (5%)	0	24 (20%)	161 (22%)	0	1 (2%)	44 (15%)
Discontinuation due to AE	4 (8.9%)	0	3 (5%)	0	11 (8.9%)	102 (14%)	1 (2%)	1 (2%)	28 (9%)

Source: Tables 2-17 to 2-18, pp99-100, and Section 2.5.2, pp96-98 of the submission; Table 12-7, p139 of the ZS004 Clinical Study Report.
Abbreviations: AE, adverse event; SZC, sodium zirconium cyclosilicate.

6.31 Overall, larger proportions of patients treated with SZC reported any adverse event and serious adverse events compared to placebo, and the proportions of patients reporting adverse events increased with longer duration of treatment.

6.32 There were similar proportions of patients reporting any adverse events between the ZS004 and OPAL-HK trials, with larger proportions of patients reporting events in the longer ZS004e, ZS005 and AMETHYST-DN studies. Larger proportions of patients treated with patiromer in the AMETHYST-DN study reported treatment related adverse events compared to SZC, while larger proportions of patients treated with SZC reported serious adverse events.

6.33 The most commonly reported adverse events by system organ class preferred term, based on the large, longer term ZS005 study (N=746), included infections and infestations (29.4%), gastrointestinal disorders (22.4%), general disorders (19.2%) and metabolism and nutrition disorders (17.3%). The most common adverse events were hypertension (11%), peripheral oedema (9.7%), urinary tract infection (7.9%) and nausea (7.5%). Small proportions of patients reported hypokalaemia (1.5%), hyperkalaemia (2.5%) or hypomagnesaemia (2.4%). Hypokalaemia was reported by 10% of patients treated with SZC 10 or 15 g once daily in ZS004, and 5.7% of patients in the ZS004e extension study.

6.34 The most commonly reported adverse events in patients treated with patiromer included hypomagnesaemia, constipation and headache. Based on a naïve comparison, larger proportions of SZC patients in the SZC 10 g and 15 g arms of the ZS004 trial reported hypokalaemia (9.8%, 10.7%), compared to patients treated with patiromer in the OPAL-HK trial (5%) and AMETHYST-DN study (2.3%); while smaller proportions of patients in the SZC ZS004e and ZS005 studies reported hypomagnesemia (2.4% and 1.2%, respectively), compared to patients in the patiromer AMETHYST-DN study (7.2%).

6.35 In the ZS004 Maintenance Phase hypokalaemia was reported in 9.8% of patients treated with SZC 10 g daily and 10.7% of patients treated with SZC 15 g daily, while patients treated with SZC 5 g or receiving placebo reported no hypokalaemia events.

In the ZS004e and ZS005, 5.7% and 1.5% (respectively) of patients reported hypokalaemia.

6.36 Comparisons of adverse events were constrained due to the limited safety data reported in the OPAL-HK and AMETHYST-DN trial publications. Additionally, the results of the comparison may have been impacted by differences in patient characteristics between the trials.

6.37 The submission presented the most recent Periodic Benefit-Risk Evaluation Report for SZC (PBRER; 8 May 2023) for the reporting period 22 March 2022 to 21 March 2023 (Attachment 2 of the resubmission). No important identified risks or potential risks or missing information related to the use of SZC were identified in the PBRER.

6.38 The First Round TGA Clinical Evaluation Report identified 3 safety risks: (i) increased risk of hypokalaemia, especially during the acute treatment phase or during haemodialysis; (ii) increased risk of oedema; and (iii) patients with pre-existing QT abnormalities receiving SZC may have an increased risk of developing prolongation of the QT interval. No clinically significant dose-related trends in QTc interval across the placebo and SZC treatment groups were reported in a supplemental QTc report.

Benefits/harms

6.39 A benefits/harms table was not presented as the submission made a claim of non-inferiority.

Clinical claim

6.40 The submission described SZC as equivalent in terms of effectiveness compared with patiromer and similar in terms of safety compared to patiromer, in the treatment of chronic hyperkalaemia.

6.41 The ESC considered that SZC was non-inferior to patiromer in terms of lowering serum potassium levels to within normal limits. The ESC considered that SZC was likely to be non-inferior in terms of enabling patients to remain on RAASi therapy, if achieving maintaining normokalaemia were accepted as appropriate surrogate outcomes for the maintenance of RAASi treatment. The ESC noted the following limitations with the clinical evidence:

- The absence of head-to-head clinical trials comparing SZC with patiromer. In addition, an indirect comparison was not appropriate given the substantial differences between the patiromer trials and SZC studies in terms of study design (study drug titration protocols, study duration, serum potassium thresholds) and population demographic and disease characteristics (chronicity of hyperkalaemia, definition of hyperkalaemia requiring pharmacological intervention, and comorbid CKD, heart failure and diabetes).
- The results of the anchored MAIC of SZC versus patiromer were considered uncertain. Matching of the selected treatment effect modifier variables in the MAIC Maintenance Phase analysis of the key outcome resulted in an effective

sample size of 42.18 (down from 150 observed), suggesting poor overlap between the trial populations and substantial data loss. In addition, it was unclear whether all relevant treatment effect variables were identified and matched in the analysis (e.g., eGFR <60mL/min/1.73 m^2).

6.42 The claim of similar safety was based on a naïve comparison of safety outcomes for SZC and patiromer. The ESC noted that the comparisons were highly constrained due to the limited details of adverse events reported in the OPAL-HK and AMETHYST-DN trial publications. Additionally, the results of the comparison may have been impacted by differences in patient characteristics between the trials (i.e., proportions of patients with CKD stage 3-4, diabetes, heart failure, treated with RAASi medicines). Noting that SZC was likely associated with a higher risk of hypokalaemia, but a lower risk of hypomagnesaemia than patiromer, the ESC considered that the claim of similar safety was likely reasonable. The ESC stated that a claim of non-inferior safety could not be supported as the evidence presented was an unanchored comparison in different populations.

6.43 The PBAC considered that SZC was likely to be non-inferior to patiromer in terms of comparative effectiveness.

6.44 The PBAC considered that the claim of similar comparative safety was reasonable, but agreed with ESC in that a claim of non-inferior safety could not be supported due to the nature of the data presented.

Economic analysis

6.45 The submission presented a cost-minimisation of SZC versus patiromer for the treatment of chronic hyperkalaemia in patients with chronic kidney disease Stage 3-4.

6.46 Table 7 summarises the key components of the cost- minimisation approach.

Table 7: Key components and assumptions of the cost-minimisation approach

Component	Claim or assumption
Therapeutic claim: effectiveness	Based on the evidence described above, the effectiveness of SZC is claimed to be equivalent to patiromer.
Therapeutic claim: safety	Based on the evidence described above, the safety of SZC is claimed to be similar to patiromer.
Evidence base	Matching-adjusted indirect comparisons between SZC and patiromer; naïve indirect treatment comparison.
Drug adherence	Assumed to be 50%, based on the adherence for patiromer included in the March 2023 patiromer submission (Patiromer PSD, March 2023 PBAC Meeting).
Equi-effective doses	SZC 3.70 g is equi-effective to patiromer 4.95 g, both taken orally once daily. Due to the flat pricing across dose strengths, the cost of treatments is determined by the number of sachets required to achieve the required dose. In terms of the average number of sachets of SZC and patiromer across dose strengths, this translates to SZC 0.50 sachets per day is equi-effective to patiromer 0.52 sachets per day (see paragraphs 6.49 to 6.51).
Direct medicine costs	SZC: AEMP $[redacted] per pack (30); $[redacted] per patient per 361.76 days.[a] Patiromer: AEMP $325.89 (30; published); $2,035.64 per patient per 361.76 days.[a] Revised in the PSCR (see paragraph 6.53 and Table 9).
Other cost offsets	Patiromer: monitoring costs (serum magnesium monitoring) $9.70 per test; $115.29 per 361.76 days.[a] Revised in the PSCR to one test per year (see paragraph 6.53 and Table 9).

Source: Table 3-1, p122 of the submission.
Abbreviations: AEMP, approved ex-manufacturer price; SZC, sodium zirconium cyclosilicate.
[a] Calculated costs and utilisation were based on the median duration of treatment with patiromer of 361.76 days, derived from Vifor Pharma's Australian Compassionate Access Program (VCAP; Table 2, paragraph 4.14, Patiromer PSD, March 2023 PBAC meeting).

6.47 The submission proposed the following equi-effective doses: SZC 3.70 g per day is equivalent to patiromer 4.95 g per day. In terms of the average number of sachets of SZC and patiromer across dose strengths, this translates to SZC 0.50 sachets per day is equi-effective to patiromer 0.52 sachets per day.

6.48 Table 8 summarises the calculation of the equi-effective doses and average number of sachets.

Table 8: Equi-effective doses

	SZC		Patiromer	
	Value	Source	Value	Source
Average daily dose	7.40 g	(5 g x 51.95%) + (10 g x 48.05%).	9.90 g	(8.4 g x 85.7%) + (16.8 g x 10.7%) + (25.2 g x 3.6%).
Adherence	50%	Patiromer PSD, March 2023 PBAC Meeting.	50%	Patiromer PSD, March 2023 PBAC Meeting.
Equi-effective daily dose	3.70 g	7.40 x 50% adherence.	4.95 g	9.90 x 50% adherence.
Sachets per day	0.50	[(51.95% x 1 5 g sachet) + (48.05% x 1 10 g sachet)] × 50% adherence.	0.52	[(85.70% x 1 sachet (8.4 g)) + (10.70% x 1 sachet (16.8 g)) + (3.60% x 2 sachets (25.2 g)] x 50% adherence.

Source: Table 3-3, p124 of the submission.
Abbreviations: PSD, Public Summary Document; SZC, sodium zirconium cyclosilicate.

6.49 The average daily SZC dose (SZC 7.40 g daily) was derived from SZC dosing data reported in the long-term ZS004e and ZS005 studies. The submission averaged the proportions of patients using the SZC 5 g and 10 g dose strengths in each study, and calculated a weighted average dose per patient per day. Using similar methodology, the average daily patiromer dose (patiromer 9.90 g daily) was derived from the patiromer compassionate access scheme, considered at the March 2023 PBAC

meeting (Table 2, Patiromer PSD, March 2023 PBAC meeting). Given the flat pricing of both agents across dose strengths, the submission estimated the equi-effective number of sachets using similar methods.

6.50 The ESC noted that the equi-effective doses were highly uncertain given the submission assumed that a proportion of patients receiving patiromer would require 2 sachets per 25.2 g dose, but all patients receiving SZC would require only 1 sachet, regardless of dose. The submission assumed that all patients in the ZS004e and ZS005 studies reporting a mean daily dose of SZC < 10 g daily would only require one 5 g sachet, and all patients reporting a mean daily dose of SZC ≥ 10 g daily would only require one 10 g sachet. Given 16 (13%) patients in ZS004e and 74 (9.9%) patients in ZS005 reported a mean dose of > 10 g daily in the extended dosing phase, the ESC considered that the assumption that no patients would be using more than one SZC 10 g sachet daily was inconsistent with the study data. Further, the ESC noted that although the draft SZC Product Information recommends a maximum SZC dose of 10 g once daily for the treatment of chronic hyperkalaemia, this was inconsistent with the dosing regimens used in the clinical studies. The claim of equivalent efficacy was based on an anchored MAIC analysis of the ZS004 study which included data from patients treated with the SZC 5 g and 10 g dose strengths (SZC 15 g dose arm excluded), and longer-term data from patients treated with SZC up to 15 g daily in the ZS004e (13% of patients) and ZS005 (9.9% of patients) studies.

6.51 The PSCR disagreed that some patients treated with SZC may receive doses requiring more than one SZC sachet (i.e. >10 g daily), stating that (i) the evidence suggested that a 15 g dose of SZC is no more effective in maintaining normokalaemia than a 5 g or 10 g dose, and (ii) dosing would be constrained by the dosing regimens recommended in the proposed Product Information. However, the ESC noted that the ZS004e and ZS005 studies titrated SZC dosing regimens (SZC 0-15 g daily) based on response to therapy and considered that this was inconsistent with the proposition that 15 g of SZC was no more effective than the 5 g and 10 g doses in some patients. Further, the ESC noted that the submission based the equi-effective dose of patiromer on the doses observed in the clinical studies. Thus, the ESC considered that the equi-effective dose of SZC should also be based on the doses observed in the clinical studies. The pre-PBAC response stated that if the doses observed in the SZC studies were used, then the doses from the patiromer studies should also be used, and that this resulted in approved ex-manufacturer prices (AEMPs) for SZC that were considerably higher than presented in the submission.

6.52 The submission claimed that a PBS listing for SZC was not expected to result in changes in resource use due to no difference in administration profiles. However, while SZC demonstrated similar safety compared to patiromer, the submission noted that treatment with patiromer may require additional serum magnesium monitoring, not required with SZC. The submission estimated the related costs of serum magnesium monitoring assuming ongoing once monthly testing, based on MBS item 66500 ($9.70 per test per month or $115.29 over 361.76 days).

6.53 The patiromer Product Information includes a precaution recommending serum magnesium should be monitored for at least 1 month after initiation of patiromer. Given some monitoring of serum magnesium would be routinely included in the management of chronic hyperkalaemia in patients with CKD stage 3-4, the evaluation considered that the frequency of serum magnesium monitoring may have been substantially overestimated. In addition, magnesium monitoring in patients treated with patiromer was not included as a cost offset in the patiromer versus SPS/CPS cost minimisation considered by the PBAC at the March 2023 meeting (Table 2, paragraph 4.14, Patiromer PSD, March 2023 PBAC meeting). The PSCR provided a revised cost minimisation approach assuming one patiromer related serum magnesium monitoring event per year ($9.70) versus 11.9 events per year ($115.29) used in the submission (see Table 9).

6.54 Results of the cost-minimisation approach presented in the submission and revised in the PSCR are presented in Table 9 below.

Table 9: Results of the cost-minimisation approach

Component	SZC	Patiromer
Submission		
Drug cost per pack (30 sachets; AEMP)	**Submission: $[redacted]** **PSCR: $[redacted]**	**$325.89**
Sachets per day assuming 50% adherence	0.50	0.52
Treatment duration (days)[a]	361.76	361.76
Sachets per pack	30	30
Packs per treatment duration [treatment duration ÷ (sachet per pack ÷ sachets per day)]	6.03	6.25
Drug cost per treatment duration [drug cost per pack × packs per treatment duration]	Submission: $[redacted] PSCR: $[redacted]	$2,035.64
Monitoring costs per treatment duration	$0.00	Submission: $115.29 PSCR: $9.70
Total cost per treatment duration [drug cost + monitoring costs]	Submission: $[redacted] PSCR: $[redacted]	Submission: $2,150.92 PSCR: $2,045.34

Source: Table 3-5, p126 of the submission and Table 2, p4 of the PSCR.
Abbreviations: PSD, Public Summary Document; SZC, sodium zirconium cyclosilicate.
a Based on the median duration of treatment with patiromer of 361.76 days, derived from Vifor Pharma's Australian Compassionate Access Program (Table 2, paragraph 4.14, Patiromer PSD, March 2023 PBAC meeting).

6.55 The revised cost minimisation estimated an AEMP for SZC of $[redacted] (dispensed price for maximum quantity (DPMQ) $[redacted]) for 30 sachets of SZC 5 g and 10 g. The ESC considered that the reduction in patiromer related serum magnesium monitoring events, as presented in the PSCR, was reasonable.

6.56 Sensitivity analyses conducted during the evaluation demonstrated that the cost-minimised price of SZC is sensitive to the assumption around the proportions of SZC and patiromer patients requiring more than one sachet per daily dose (see Table 10).

Table 10: Sensitivity analyses for the cost-minimisation (published price)

Sensitivity analysis	AEMP of SZC - submission	AEMP of SZC - PSCR
Base case	$	$
Sensitivity analyses		
Assuming use of SZC 15 g daily as reported in the ZS004e (and ZS005 studies (i.e., 5 g 51.95%; 10 g 36.59%; 15 g 11.46%)	$	$
Assuming no cost offset for serum magnesium monitoring	$	$
Assuming equi-effective dose of SZC 0.52 sachets = patiromer 0.52 sachets	$	$
Assuming equi-effective dose of SZC 0.52 sachets = patiromer 0.52 sachets and no cost offset for serum magnesium monitoring	$	$
Assuming use of SZC 15 g daily as reported in the ZS004e and ZS005 studies and no cost offset for serum magnesium monitoring	$	$

Source: Calculated during the evaluation and from the PSCR
AEMP = approved ex-manufacturer price; SZC = sodium zirconium cyclosilicate

Drug cost/patient/course

6.57 The same assumptions were used in estimating the costs of SZC and patiromer in the cost-minimisation approach and financial implications, based on estimates included in the March 2023 patiromer submission.

6.58 The revised cost per patient per course of SZC is $ (based on the revised DPMQ of $, an assumption that patients receive one 5 g or 10 g sachet per dose, with 50% adherence and a treatment duration of 11.9 months).

6.59 The cost per patient per course of patiromer is $2,317.18 (based on the assumption that 96.4% of patients require one 8.4 g or 16.8 g sachet per dose and 3.6% of patients require a 25.2 g dose (requiring a sachet of patiromer 8.4 g and a sachet of patiromer 16.8 g), a DPMQ of $375.91, with 50% adherence and a treatment duration of 11.9 months).

Estimated PBS usage & financial implications

6.60 This submission was not considered by DUSC.

6.61 The submission used a mixed epidemiological/market share approach to estimate the utilisation and financial impact associated with the PBS/RPBS listing of SZC for the treatment of adults with chronic hyperkalaemia and CKD stage 3-4 treated with RAASi medicines or unable to tolerate a RAASi medicine due to prior occurrence of hyperkalaemia.

6.62 The budget impact model was based on inputs and methodologies used in the patiromer submission (Table 4, Patiromer PSD, March 2023 PBAC meeting) as the requested restriction for SZC is consistent with the current listing for patiromer. The submission stated that the sponsor expects 50% of patients treated with patiromer would instead be treated with SZC, assuming no market growth associated with the listing of SZC. As the second drug in this setting, if recommended, the ESC considered that that the addition of SZC would likely result in market growth in an area of previous unmet need and likely increased physician awareness of therapeutic options. The sources used to derive the financial estimates are presented in Table 11 below.

Table 11: Data sources and parameter values applied in the utilisation and financial estimates

Parameter	Value applied and source	Comment
Treated population		
Prevalence of CKD Stage 3+	5.72% in Year 1 increasing to 6.27% in Year 6 (0.11% yearly increase). Based on the prevalence of CKD 3-5 reported in the 2011-2012 National Health Measures Survey for all ages (4.4%, AIHW 2018).	This was consistent with the March 2023 patiromer submission.
CKD diagnosis rate	50%. Assumption.	This was consistent with the March 2023 patiromer submission.
Patients with CKD Stage 3-4	98.2%. Based on a retrospective review of Australian general practice data (January 2013 to June 2017) to assess the incidence of hyperkalaemia in CKD patients using RAASi therapy as well as any changes in RAASi therapy (Jun 2019). Patients were excluded if they had a prior diagnosis of hyperkalaemia, were not on a RAASi at baseline or had end stage kidney disease. The submission used the complement of the baseline proportion of patients with recorded eGFR <15 mL/min/1.73m^2 (1.8%).	This was consistent with the March 2023 patiromer submission.
Patients with ≥2 hyperkalaemia episodes in 12 months	1.29%. Calculated as a weighted estimate (87% x 0.9% + 13% x 3.8%) using data from two studies described below. Sriperumbuduri 2021. A Canadian retrospective cohort study of the initial and 1-year recurrent risk of hyperkalaemia (K+ ≥5.5 mEq/L) in older adults (≥66 years old) without a recent episode of hyperkalaemia (conducted between 2008 and 2015). Patients with kidney failure (with or without renal replacement therapy) were excluded. The study reported the risk of 1 or more recurrent hyperkalaemia events of 0.9% and 3.8% in those with an eGFR of 30 to 59 and <30 mL/min/1.73m^2, respectively. Jun 2019 (as above). The distribution of CKD stage 3 and 4 patients was estimated as 87% and 13%, respectively.	This was consistent with the March 2023 patiromer submission.
Patients on RAASi treatment	100%. Assumption	This was consistent with the March 2023 patiromer submission.
Treatment uptake rate	10% in Year 1 increasing to 50% in Year 6 (8% yearly increase). Assumed uptake rate for patiromer.	This was consistent with the March 2023 patiromer submission.
Treatment utilisation		
SZC market share	[redacted]%. Assumption.	-
SZC/patiromer adherence rate	50%. Assumed to be equivalent to adherence estimates for patiromer used in the March 2023 patiromer submission.	Given dosing data from ZS004e and ZS005 accounted for adherence in the trial setting, the application of an additional assumed 50% adherence rate may have overestimated treatment discontinuations likely to be realised in clinical practice. As a similar approach was applied to both SZC and patiromer, the impact of this assumption may be small.
SZC/patiromer treatment duration	11.9 months. Assumed to be equivalent to the treatment duration for patiromer used in the March 2023 patiromer submission.	Given mean duration of treatment was not reported in the SZC studies, the use of the patiromer treatment duration for both treatments may be reasonable.

Parameter	Value applied and source	Comment
SZC dose distribution	51.95% on 5 g and 48.05% on 10 g. Based on the average of dose distributions in the ZS004e and ZS005 trials assuming patients using 15 g daily in those trials would instead use 10 g daily as per the maximum recommended dose for maintenance therapy in the draft product information.	The assumed dose distributions underestimated the use of the SZC 10 g dose strength. As 16 (13%) patients in the of ZS004e and 74 (9.9%) patients in ZS005 reported a mean dose of >10 g daily in the extended dosing phases, the exclusion of the SZC 15 g dose strength was not appropriate.
SZC scripts per patient	6.03 per patient. Calculated as 12.06 scripts required for 11.9 months of treatment (average daily dose 7.4 g), adjusted for 50% adherence.	Given the calculated number of scripts per patient was based on the SZC dose distribution and an assumed adherence of 50%, the estimated number of scripts per patient is underestimated.
Patiromer dose distribution	85.7% on 8.4 g, 10.7% on 16.8 g and 3.6% on 25.2 g. Based on the March 2023 patiromer submission. Estimated from an analysis of the patiromer compassionate access program.	-
Patiromer scripts per patient	6.25 per patient. Calculated as 12.49 scripts required for 11.9 months of treatment (average daily dose 9.9 g), adjusted for 50% adherence.	-
Serum magnesium monitoring for patients on patiromer	11.9 services per patient per year. Based on assumed monthly frequency of monitoring over the estimated 11.9 months duration of treatment.	The assumed frequency of monitoring was inadequately justified based on recommendations in the product information of patiromer suggesting monitoring for at least 1 month for patients starting treatment, and ongoing monitoring in patients with decreasing magnesium levels. The PSCR revised this to assume one magnesium monitoring event per year.

Source: Table 4-1, p128 of the submission; patiromer PSD March 2023 PBAC meeting; patiromer PSD November 2022 PBAC meeting
Abbreviations: CKD, chronic kidney disease; DPMQ, dispensed price maximum quantity; RAASi, renin-angiotensin-aldosterone system inhibitor; SZC, sodium zirconium cyclosilicate

6.63 The estimated net cost to the PBS/RPBS of listing SZC is presented in Table 12.

Table 12: Estimated net cost of SZC to the PBS/RPBS/MBS

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Submission						
Estimated extent of use						
Patients treated with SZC	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
SZC scripts	[redacted][2]	[redacted][2]	[redacted][3]	[redacted][3]	[redacted][4]	[redacted][4]
Estimated financial implications of SZC						
SZC cost to PBS/RPBS cost less copayments	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]
Estimated financial implications for patiromer						
Patiromer cost to PBS/RPBS less copayments	-$[redacted][6]	-$[redacted][6]	-$[redacted][6]	-$[redacted][6]	-$[redacted][6]	-$[redacted][6]
Net financial implications						
Net cost to PBS/RPBS	**$[redacted][5]**	**$[redacted][5]**	**$[redacted][5]**	**$[redacted][5]**	**$[redacted][5]**	**$[redacted][5]**
MBS cost offsets due to reduced serum magnesium monitoring	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]
Net PBS/RPBS/MBS cost	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]
PSCR revised financial implications						
Net cost to PBS/RPBS	**$[redacted][5]**	**$[redacted][5]**	**$[redacted][5]**	**$[redacted][5]**	**$[redacted][5]**	**$[redacted][5]**
MBS cost offsets due to reduced serum magnesium monitoring	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]
Net PBS/RPBS/MBS cost	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]

Source: Tables 4-2 to 4-9, pp132-135; Table 4-14, p139 of the submission; Table 3, p4 of the PSCR
Abbreviations: CKD, chronic kidney disease; RAASi, renin-angiotensin-aldosterone system inhibitor; SZC, sodium zirconium cyclosilicate
The redacted values correspond to the following ranges:
[1] *< 500*
[2] *500 to < 5,000*
[3] *5,000 to < 10,000*
[4] *10,000 to < 20,000*
[5] *$0 to < $10 million*
[6] *net cost saving*

6.64 The estimated net cost to the PBS/RPBS for SZC including cost offsets associated with substituted use of patiromer was $0 to < $10 million in Year 1, increasing to $0 to < $10 million in Year 6, a total of $0 to < $10 million over 6 years. The revised estimates in the PSCR resulted in a net cost in Year 1 of $0 to < $10 million, increasing to $0 to < $10 million in Year 6 and totalling $0 to < $10 million over the first 6 years of listing.

6.65 The small net PBS/RPBS cost associated with SZC in financial estimates was due to the higher proposed DPMQ of SZC compared to patiromer.

Quality Use of Medicines

6.66 The submission noted that the sponsor is planning education activities to ensure appropriate and best practice with respect to prescribing.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC recommended the listing of sodium zirconium cyclosilicate (SZC) on the basis that it is available as a General Schedule Authority Required (telephone/online) for the treatment of chronic hyperkalaemia in patients with chronic kidney disease

(CKD) Stage 3-4. The PBAC accepted that SZC was likely non-inferior in terms of efficacy, and similar in terms of safety, to patiromer. The PBAC considered that a cost minimisation approach between SZC and patiromer was appropriate and considered that the addition of SZC to the PBS should not result in any additional cost to Government.

7.2 The PBAC acknowledged the consumer comments relating to SZC which described the benefits of treatment and the need for alternate therapies in this setting.

7.3 The PBAC considered that the treatment algorithm that positioned SZC as an alternative to patiromer in the treatment of hyperkalaemia in patients with CKD Stage 3-4 was reasonable.

7.4 The PBAC noted that, based on the results of the ZS004 trial, SZC maintained significantly lower serum potassium values compared to placebo over the 29-day trial period. The PBAC noted that SZC patients remained normokalaemic for up to a year in the extension studies, with rebound increases in serum potassium when patients ceased treatment at end-of-study.

7.5 As there was no head-to-head comparison of SZC and patiromer, the PBAC noted that the submission presented an anchored matching-adjusted indirect comparison (MAIC) with placebo as the common reference, based on the ZS004 SZC trial and the OPAL-HP patiromer trial. Unanchored MAICs were presented as supporting evidence. The PBAC noted that SZC patients reported similar mean potassium values compared to patiromer, although noting that there were substantial differences between the trials in terms of study duration, drug dose titration and study objectives that meant that the results should be interpreted with caution.

7.6 Overall, the PBAC considered that SZC was likely non-inferior to patiromer in terms of the treatment of chronic hyperkalaemia. The PBAC also considered that maintaining normokalaemia was an appropriate surrogate outcome for the maintenance of RAASi treatment, and thus, SZC was likely non-inferior to patiromer in terms of enabling patients to remain on RAASi therapy.

7.7 The PBAC noted that SZC was associated with higher rates of any adverse event and serious adverse events compared to placebo, and that the most commonly reported adverse events in SZC-treated patients were hypertension, peripheral oedema and urinary tract infection. Although the comparison of adverse events was constrained by the limited safety data reported in the patiromer publications, the PBAC noted that SZC was likely associated with a higher rate of hypokalaemia, but a lower risk of hypomagnesaemia than patiromer.

7.8 Overall, the PBAC considered that the safety profile of SZC was likely similar to patiromer, but that a claim of non-inferiority could not be supported due to the nature of the data presented, i.e., an unanchored comparison in different populations.

7.9 The PBAC considered that a cost minimisation approach was acceptable given the non-inferiority claim between SZC and patiromer. The PBAC noted that the submission

proposed that 0.5 sachets of SZC was equi-effective to 0.52 sachets of patiromer, which was based on the average daily doses and an adherence of 50%. Noting the uncertainties with the calculation of the equi-effective doses (see paragraph 6.50) and given the flat pricing of both agents across dose strengths, the PBAC considered that the more appropriate equi-effective doses were:

1 sachet of SZC (either 5 g or 10 g) = 1 sachet of patiromer (either 8.4 g or 16.8 g)

7.10 In addition, the PBAC considered that the cost offsets for magnesium monitoring should not be included, as serum monitoring would be routinely performed in the management of CKD patients.

7.11 The PBAC noted that the utilisation and financial impact estimates for SZC were based on those presented previously for patiromer. Noting that SZC would substitute for patiromer, the PBAC considered that there should be no additional cost to the PBS associated with the listing of SZC.

7.12 The PBAC recalled that as there was some uncertainty with the financial estimates for patiromer, it has requested that the usage of patiromer be reviewed by the DUSC two years after listing. The PBAC advised that SZC utilisation should be included in that review.

7.13 The PBAC considered that the minor amendments to the proposed initial and continuing restrictions to align them with the current listings for patiromer were appropriate.

7.14 The PBAC advised that SZC is suitable for prescribing by nurse practitioners for continuing treatment only.

7.15 The PBAC recommended that SZC should not be exempt from the Early Supply Rule.

7.16 The PBAC advised that, under Section 101(3BA) of *the National Health Act 1953*, SZC should not be treated as interchangeable with any other drugs on an individual patient basis.

7.17 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because SZC is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over patiromer, and not expected to address a high and urgent unmet clinical need, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.

7.18 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
SODIUM ZIRCONIUM CYCLOSILICATE					
Sodium zirconium cyclosilicate hydrate, 5g powder for oral liquid, 30 sachets	NEW	1	30	5	Lokelma
Sodium zirconium cyclosilicate hydrate, 10g powder for oral liquid, 30 sachets	NEW	1	30	5	Lokelma

Restriction Summary [new] / Treatment of Concept: [new]	
Concept ID (for internal Dept. use)	**Category / Program:** GENERAL – General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒ Authority Required (telephone/electronic via PBS Authorities system)
	Administrative advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333
	Administrative advice: Special pricing arrangements apply
	Indication: Chronic hyperkalaemia
	Treatment Phase: Initial PBS subsidised treatment
	Population criteria:
	Patient must have stage 3 to stage 4 chronic kidney disease
	Clinical criteria:
	The condition must be inadequately controlled by a low potassium diet,
	AND
	Clinical criteria:
	Patient must have experienced at least 2 episodes of hyperkalaemia (defined as serum potassium levels of at least 6.0 mmol/L) within the 12 months prior to commencing this drug,
	AND
	Clinical criteria:
	The treatment must not be in place of emergency treatment of hyperkalaemia.
	AND
	Clinical criteria:
	Patient must be undergoing treatment with a renin angiotensin aldosterone system inhibitor; OR
	Patient must be indicated for treatment with a renin angiotensin aldosterone system inhibitor; but ~~not able~~ unable to tolerate this due to prior occurrence of hyperkalaemia,
	Treatment criteria:
	Must be treated by a specialist medical practitioner with experience in the diagnosis and management of chronic kidney disease.

MEDICINAL PRODUCT medicinal product pack		PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
SODIUM ZIRCONIUM CYCLOSILICATE						
Sodium zirconium cyclosilicate hydrate, 5g powder for oral liquid, 30 sachets		NEW	1	30	5	Lokelma
Sodium zirconium cyclosilicate hydrate, 10g powder for oral liquid, 30 sachets		NEW	1	30	5	Lokelma
Restriction Summary [new] / Treatment of Concept: [new]						
Concept ID (for internal Dept. use)	**Category / Program:** GENERAL – General Schedule (Code GE)					
	Prescriber type: ☒ Medical Practitioners					
	Prescriber type: ☒ Nurse practitioners					
	Restriction type: ☒ STREAMLINED					
	Administrative advice: Special pricing arrangements apply					
	Administrative advice: Continuing Therapy Only: For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.					
	Indication: Chronic hyperkalaemia					
	Treatment Phase: Continuing treatment					
	Clinical criteria:					
	Patient must have previously received PBS-subsidised treatment with this drug for this condition					
	AND					
	Clinical criteria:					
	The treatment must not be in place of emergency treatment of hyperkalaemia.					
	AND					
	Clinical criteria:					
	Patient must be undergoing treatment with a renin angiotensin aldosterone system inhibitor					
	Treatment criteria:					
	Patient must not be undergoing dialysis					

This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available

through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor had no comment.