sodium zirconium cyclosilicate powder for oral suspension (Lokelma®)

AstraZeneca UK Ltd

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The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and, following review by the SMC executive, advises NHS Boards and Area Drug and Therapeutics Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

sodium zirconium cyclosilicate (Lokelma®) is accepted for restricted use within NHSScotland.

Indication under review: treatment of hyperkalaemia in adult patients.

SMC restriction: patients with persistent hyperkalaemia (defined as a serum potassium of 5.5 to 6.0 mmol/L) with chronic kidney disease (CKD) stage 3b to 5 and/or heart failure, who would otherwise need to down-titrate or discontinue their renin-angiotensin-aldosterone system inhibitor (RAASi) therapy to maintain a clinically acceptable serum potassium level (normokalaemia).

Sodium zirconium cyclosilicate, compared with placebo, reduced serum potassium in two and four-week studies in adults with hyperkalaemia. In an uncontrolled one-year study sodium zirconium cyclosilicate supported normal serum potassium in a majority of adults with hyperkalaemia.

SMC has previously issued advice for sodium zirconium cyclosilicate for the treatment of hyperkalaemia (defined as a serum potassium of >6.0mmol/L) in adult patients with CKD stage 3b to 5 and/or heart failure, who would otherwise need to down-titrate or discontinue their renin-angiotensin-aldosterone system inhibitor therapy to maintain a clinically acceptable serum potassium level (normokalaemia) (SMC2288) and in the emergency care setting for the treatment of acute, life-threatening hyperkalaemia alongside standard care (SMC2515). These pieces of advice are still valid.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Sodium zirconium cyclosilicate is an orally administered non-polymer inorganic cation exchange crystalline compound. It is not absorbed from the gastro-intestinal tract where it captures potassium cations in exchange for hydrogen and sodium cations, thereby reducing the amount of absorbable free potassium, increasing faecal excretion of potassium and decreasing serum potassium. In the treatment of hyperkalaemia (high serum potassium) it is given orally, as a suspension in water, at a dose of 10 g three time a day, initially, and patients usually achieve normal potassium levels within one to three days. It can then be given as maintenance at the minimum effective dose to prevent recurrence of hyperkalaemia (up to the maximum of 10 g once daily). See summary of product characteristics for further information.[1]

1.2. Disease background

Angiotensin converting enzyme inhibitor, angiotensin receptor blocker, mineralocorticoid receptor antagonist, or angiotensin receptor-neprilysin inhibitor, which are renin-angiotensin-aldosterone system inhibitor (RAASi) therapies, are recommended for the treatment of chronic kidney disease (CKD) and heart failure.[2-6] Patients receiving RAASi therapy for these conditions may develop hyperkalaemia as a side effect. There is no agreed definition of hyperkalaemia. The European Resuscitation Council defines it as a serum potassium level ≥5.5 mmol/L, with mild elevations defined as 5.5 to 5.9 mmol/L, moderate 6.0 to 6.4 mmol/L and severe ≥6.5 mmol/L. The level at which treatment is initiated can be influenced by clinical considerations, including co-morbidities.[7, 8]

1.3. Company proposed position

The submitting company has requested that SMC considers sodium zirconium cyclosilicate when positioned for use in adults with persistent hyperkalaemia that have a serum potassium concentration 5.5 to 6.0 mmol/L, and have heart failure and/or CKD, stage 3b to 5, who would otherwise need to down-titrate or discontinue their RAASi therapy to maintain normokalaemia. This would extend the current SMC restriction from serum potassium >6.0mmol/L to ≥5.5 mmol/L.

1.4. Treatment pathway and relevant comparators

Guidelines suggests that hyperkalaemia associated with RAASi therapy be managed by measures to reduce serum potassium levels rather than decreasing the dose or stopping RAASi.[2, 9] The Kidney Disease Improving Global Outcomes (KDIGO) guidelines note that these could include a review of concurrent medicines, moderating dietary potassium intake and use of diuretics, sodium bicarbonate or potassium binders.[2] In September 2020 and August 2021, SMC has published advice (SMC2288 and SMC2381) that the potassium binders, sodium zirconium cyclosilicate and patiromer sorbitex calcium, are accepted for restricted use within NHS Scotland for treatment of hyperkalaemia in adult patients, with a restriction to patients with hyperkalaemia (defined as a serum potassium of >6.0mmol/L) with CKD stage 3b to 5 and/or heart failure, who would otherwise need to down-titrate or discontinue their RAASi therapy to maintain a clinically acceptable serum potassium level (normokalaemia).

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence is from the ZS-003, ZS-004 and ZS-005 studies.[8, 10-14]

Table 2.1. Overview of relevant studies.[8, 10-14]

Criteria	ZS-003	ZS-004:
Study design	Multi-centre, double-blind, phase III.	Multi-centre, double-blind, phase III.
Eligible patients	Adults with serum potassium 5.0 to 6.5 mmol/L.	Adults with serum potassium ≥5.1 mmol/L.
Treatments and randomisation	**Acute phase**: randomised equally to double-blind placebo or sodium zirconium cyclosilicate 1.25g, 2.5g, 5g or 10g three times daily for two days. **Maintenance phase**: patients given sodium zirconium cyclosilicate who had serum potassium 3.5 to 4.9 mmol/L were re-randomised equally to their original dose of sodium zirconium cyclosilicate each morning or placebo for 12 days. Placebo group randomised equally to sodium zirconium cyclosilicate 1.25g or 2.5g once daily for 12 days.	**Acute phase**: open-label oral sodium zirconium cyclosilicate 10g three times daily for two days. **Maintenance phase**: patients who had normal serum potassium (3.5 to 5.0 mmol/L) were randomised in a 7:4:4:4 ratio to double-blind treatment with placebo or sodium zirconium cyclosilicate 5g, 10g or 15g once daily for 28 days.
Primary outcome	**Acute phase**: proportion with normal serum potassium (3.5 to 4.9 mmol/L) within 48 hours. **Maintenance phase**: cumulative number of days maintaining normal potassium in the randomised withdrawal groups.	**Maintenance phase**: least square mean serum potassium over days 8 to 29 of double-blind treatment.
Statistical analysis	Efficacy assessed in treated patients with at least one post-baseline assessment during relevant phase.	Efficacy assessed in treated patients with at least one post-baseline assessment during relevant phase.

In ZS-003, the primary outcome in the acute phase, the proportion who achieved normal serum potassium (3.5 to 4.9 mmol/L) within the initial 48 hours, was significantly greater versus placebo in the sodium zirconium cyclosilicate 10g, 5g and 2.5g groups, but not the 1.25g group. The primary outcome in the maintenance phase, cumulative number of days with normal serum potassium, was significantly greater in patients who continued on sodium zirconium cyclosilicate compared with those re-randomised to placebo in the 10g, 5g, and 2.5g groups, but not in the 1.25g group. In ZS-004, the primary outcome, mean serum potassium during days 8 to 29 of the maintenance phase, was significantly lower in the sodium zirconium cyclosilicate 15g, 10g and 5g groups, compared with placebo.[8, 10-13]

An open-label study, ZS-005, recruited adults with serum potassium ≥5.1 mmol/L and those who achieved normal potassium (3.5 to 5.0 mmol/L) after one to three days of oral sodium zirconium cyclosilicate 10 g three times a day and continued at a once daily dose of 5 g to 15 g titrated to maintain normal serum potassium for one year. The primary outcomes, proportions who achieved normal serum potassium at the end of the acute phase and between 3 to 13 months in the maintenance phase, are detailed in Tables 2.2 and 2.3 together with results of ZS-003 and ZS-004.[8, 10-14]

Table 2.2: Proportion of patients with normal serum potassium at end of acute phase in ZS-003, ZS-004 and ZS-005 studies.[8, 14]

	ZS-003		ZS-004	ZS-005
	Placebo	SZC 10g TID	SZC 10g TID	SZC 10g TID
Normal serum potassium	48% (75/157)	86% (121/140)[a]	88% (221/251)	78% (583/748)

Acute phase was two days in ZS-003 and ZS-004 and up to three days in ZS-005. [a] primary outcome, p<0.001 versus placebo in ZS-003; SZC = sodium zirconium cyclosilicate; TID = three times daily.

Table 2.3: Primary and secondary outcomes in maintenance phase of ZS-003, ZS-004 and ZS-005 studies.[8, 10-14]

	N	Normal potassium at end of treatment	Patients with mean serum potassium ≤5.1mmol/L	Mean days with normal potassium	Mean serum potassium (mmol/L)
ZS-003		**Day 14**	**Over days 3 to 14**		
SZC 10g once daily	63	82% (50/61)		10.2 [b]	
Placebo	61	57% (33/58)		8.2	
SZC 5g once daily	65	75% (45/60)		9.0 [b]	
Placebo	68	48% (32/66)		6.0	
ZS-004		**Day 29**	**Over days 8 to 29**		
SZC 10g once daily	51	81% (31/38)[a]	90% (45/50)[b]	13.9	4.5
SZC 5g once daily	45	67% (26/39)[b]	80% (36/45)[b]	13.4	4.8
Placebo	85	51% (37/73)	46% (38/82)	7.4	5.1
ZS-005		**Day 365**	**Over days 85 to 365**		
SZC 5g to 15g once daily[A]	743	87% (383/439)	88% (571/646)		4.7

SZC = sodium zirconium cyclosilicate. A = dose titrated to maintain normal serum potassium. [a] p<0.01 versus placebo, [b] p≤0.001 versus placebo.

2.2. Evidence to support the positioning proposed by the submitting company

The submitting company has requested that SMC considers sodium zirconium cyclosilicate when positioned for use in adults with persistent hyperkalaemia, serum potassium level between 5.5 and 6.0 mmol/L, and heart failure and/or CKD, stage 3b to 5, who would otherwise need to down-titrate or discontinue their RAASi therapy to maintain normokalaemia. Hyperkalaemia was defined as potassium ≥5.0 mmol/L in ZS-003 and ≥5.1 mmol/L in ZS-004 and ZS-005. However, many of the patients had mildly elevated serum potassium, with 77% of patients in ZS-003 having a potassium 5.0mmol/L to 5.5mmol/L and in the ZS-004 and ZS-005 studies 46% and 38% of patients had serum potassium <5.5 mmol/L at baseline. In ZS-003, ZS-004 and ZS-005 many patients had CKD, 62%, 66% and 68%, respectively, with 40%, 36% and 38% having heart failure. Also, most patients were receiving RAASi therapy: 67%, 70% and 70%, respectively. Within these studies subgroup analyses in patients with (1) CKD, (2) heart failure and (3) on RAASi treatment were generally consistent with the total study populations.[10-14] Subgroup analyses in the proposed positioning under review have not been provided.

2.3. Health-related quality of life outcomes

There were no patient reported outcomes in studies ZS-003, ZS-004 and ZS-005.

2.4. Supportive studies

A retrospective, observational analysis (ZORA) of health claims in the US, Japan and Spain included data from initial availability of sodium zirconium cyclosilicate in the respective countries (July 2019, May 2020 and June 2021) to December 2022 for adults with heart failure and/or CKD (but not on dialysis) who had received a RAASi prescription within 120 days prior to the index date. The first prescription of sodium zirconium cyclosilicate (which was known or presumed to be for an episode of hyperkalaemia) was the index date in the cohort that received this medicine. Compared with propensity score matched controls who had an episode of hyperkalaemia (index date) but did not receive a potassium binder in the following 180 days, a greater proportion of those who received sodium zirconium cyclosilicate maintained or up-titrated their RAASi therapy six months after the index date: 69% versus 53% in the US; 80% versus 56% in Japan: and 70% versus 48% in Spain.[15]

A retrospective observational analysis (SPARK) included data from adults in the UK Clinical Practice Research Datalink (CPRD) with a diagnosis of hyperkalaemia, use of a potassium binder or a serum potassium measurement between 1 January 2016 and 1 January 2019. The index date was defined as date of the latest serum potassium measurement within this period. Patients were followed until exit from the database (loss to follow-up), death or end of database period (last data collection date). Within the cohort with prior heart failure and no CKD and the cohort with prior CKD and no heart failure, regression models suggested a U-shaped association between serum potassium at the index event and the outcomes: death, hospitalisation within one year, and major adverse cardiovascular event (MACE), which included the outcomes: arrythmia, myocardial infarction, stroke, and heart failure exacerbation. That is, rates of these outcomes appeared higher in patients with serum potassium lower (<3.5 mmol/L) or higher (>5.5 mmol/L) than the normal range.[16]

*Other data were also assessed but remain confidential.**

3. Summary of Safety Evidence

Sodium zirconium cyclosilicate is a cation exchange compound that binds potassium cations in the gastro-intestinal tract in exchange for hydrogen and sodium cations. This pharmacology could be associated with adverse events of low serum potassium (hypokalaemia) and increased sodium absorption which would be associated with fluid overload (hypervolaemia). In clinical studies, sodium zirconium cyclosilicate has been associated with oedema-related adverse events, including hypervolaemia, generalised and peripheral oedema.[1]

Across the two and four-week ZS-003 and ZS-004 placebo-controlled studies rates of adverse events were similar in the sodium zirconium cyclosilicate and placebo groups. The most common adverse events were gastro-intestinal in ZS-003, with the most common, diarrhoea, reported by <5% of patients. In ZS-004 the most common adverse events were oedema, reported in the sodium zirconium cyclosilicate 5g and 10g groups by 2.2% and 5.9% versus 2.4% with placebo and low serum potassium, reported by 0 and 9.8% versus 0, respectively. In the single-arm one-year study, ZS-005, adverse events that were considered related to study drug and occurred in at least 1% of patients were constipation (3.1%), nausea (1.7%) and peripheral oedema (1.7%).[8, 14]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- Across the sodium zirconium cyclosilicate studies the primary outcomes differed, although they all assessed serum potassium levels. For sodium zirconium cyclosilicate 10g three times daily (the licensed dose for the correction phase), evidence was available from studies ZS-003, ZS-004 and ZS-005. These demonstrated that it resulted in normal serum potassium levels in 86%, 88% and 78% of patients at the end of an acute phase lasting two days in ZS-003 and ZS-004 and up to three days in ZS-005 (primary outcomes in ZS-003 and ZS-005).[8, 10-14]
- In the maintenance phase (after acute hyperkalaemia had resolved), the majority of patients given sodium zirconium cyclosilicate maintained serum potassium within the normal range in studies up to one year's duration.[8, 10-14]
- The ZORA analysis suggests that use of sodium zirconium cyclosilicate is associated with maintenance or up-titration of RAASi dose after patients have recorded an episode of hyperkalaemia.[15]

4.2. Key uncertainties

- There was no subgroup analysis in patients within the proposed positioning, that is adults with persistent hyperkalaemia, serum potassium 5.5 to 6.0 mmol/L, heart failure and/or CKD, stage 3b to 5, who would otherwise need to down-titrate or discontinue their RAASi therapy to maintain normokalaemia. However, substantial proportions of the ZS-003, ZS-004 and ZS-005 studies had CKD and were receiving RAASi therapy and many had heart failure. Also, subgroup analyses by CKD, heart failure and RAASi were generally consistent with the total study populations.[10-14]
- There is no estimate of the magnitude of any benefit of sodium zirconium cyclosilicate on the long-term outcomes such as mortality and MACE. SPARK suggested an association between a single serum potassium level and hospitalisation, MACE, and mortality.[16] However, this does not establish causation or provide evidence that altering serum potassium with sodium zirconium cyclosilicate would change these outcomes.
- Substantial proportions of patients in the three studies had mildly elevated serum potassium, with 77% of patients in ZS-003 having a serum potassium of 5.0mmol/L to 5.5mmol/L and in the ZS-004 and ZS-005 studies 46% and 38% of patients had serum potassium <5.5 mmol/L at baseline.[8, 10-14]

4.3. Clinical expert input

Clinical experts consulted by SMC considered that sodium zirconium cyclosilicate fills an unmet need in this therapeutic area where there are no alternative treatments for hyperkalaemia within the serum potassium range 5.5 to 6.0 mmol/L. They considered that it is a therapeutic advancement as it allows RAASi therapy to be optimised in these patients by treating the hyperkalaemia.

5. Summary of Patient and Carer Involvement

The following information reflects the views of the specified Patient Groups.

- We received patient group submissions from Kidney Research UK and Kidney Care UK. Both organisations are registered charities.
- Kidney Research UK has received 5.3% pharmaceutical company funding in the past two years, including from the submitting company. Kidney Care UK has received 3.6% pharmaceutical company funding in the past two years, including from the submitting company.
- Hyperkalaemia places a substantial day-to-day burden on patients' lives causing them to experience ongoing stress managing their potassium levels and fear of serious consequences. Managing hyperkalaemia in the context of CKD requires a careful balance of dietary management, medication adjustments and regular monitoring of bloods. Patients with CKD and hyperkalaemia often describe the fear, confusion, anxiety and exhaustion they experience as a result.
- A medicine that could potentially quickly and significantly lower high blood potassium levels and could help maintain potassium levels within a normal range after they have been lowered has the potential of improving a patient's quality of life, day-to-day living, physical and psychological wellbeing. New treatments that are effective and well-tolerated could improve social participation and reduce feelings of being judged or restricted.
- Caring for someone with CKD and hyperkalaemia can have a substantial emotional, physical and financial impact. This medicine could potentially help to reduce some of the burden of caring.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The economic analysis is detailed in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost utility analysis.
Time horizon	Lifetime (80 years with maximum patient age of 100) or until renal replacement therapy initiation.
Population	The patient population included in the model comprises adults with persistent hyperkalaemia with a serum potassium of 5.5 to 6.0 mmol/L. Note the previous submission (SMC2288) looked at patients with serum potassium of >6.0 mmol/L. Patients in the model have a co-diagnosis of hyperkalaemia and an underlying condition, including: • CKD stage 3a–5 (CKD stage 3b–5 in the base case) or • Heart failure (HF), New York Heart Association (NYHA) functional class I, II, III or IV.
Comparators	No targeted therapy is administered for standard care; this is justified as there are currently no pharmacological treatments accepted for use in Scotland for this patient population.

	Patients would otherwise need to down-titrate or discontinue their RAASi therapy to maintain a clinically acceptable serum potassium level (normokalaemia). Subsequently, three relevant states are included in the model to reflect different levels of RAASi use. Although there is no active treatment in the standard of care (SOC) arm, there is the accrual of hyperkalaemia management, HF, CKD, MACE, hospitalisation, and RAASi which result in costs.
Model description	The model structure covered a broad range of health states relating to the underlying disease (HFNYHA I – NYHA IV; CKD: CKD3b – CKD5), treatment-related factors (RAASi changes, treatment-related adverse events and treatment initiation/discontinuation), adverse clinical outcomes (hyperkalaemic events ['severe' or 'less severe', cardiovascular events, hospitalisation) and a number of absorbing health states (background mortality, HF mortality, CKD mortality and receipt of renal replacement therapy [RRT])
Clinical data	The key clinical efficacy data for sodium zirconium cyclosilicate come from ZS-004 for standard care versus sodium zirconium cyclosilicate , and ZS-005 for long-term use of sodium zirconium cyclosilicate.[10-14] Each patient has a unique serum potassium trajectory, while the base assumptions for serum potassium thresholds for initiating treatment, initiating re-treatment and defining "less severe" hyperkalaemia event were set at 5.5 mmol/L based on clinical expert input. Other sources of evidence include: - ZORA (Likelihood of maintained optimised RAASi therapy at six months following an incident hyperkalaemia among patient treated with sodium zirconium cyclosilicate or standard care, stratified by serum potassium levels.) - Go et al (Baseline cardiovascular disease [CVD], hospitalisation and mortality event rate in CKD patients) - SPARK (Incidence rate ratio for MACE, hospitalisation and mortality in CKD patients) - Xie et al (Mortality for "max" RAASi vs no RAASi, and CV event "max" RAASi vs no RAASi) - Yao et al (Probabilities of changes in NYHA classification per cycle) - Ford, Flather and Chen et al (Per-cycle probability of hospitalisation for HF and mortality) - Levy et al (Seattle Heart Failure Model [SHFM] hazard ratios for survival in HF patients)
Extrapolation	In the patient simulation model, the progression of CKD was modelled through CKD stages, via continuous eGFR decline until the incidence of End-Stage Renal Disease (ESRD), while the progression of HF was modelled according to transitions between NYHA classes I–IV. Patients move through key model health states for CKD and HF. The progression of HF patients is modelled via transitions between NYHA classifications (I–IV), using monthly probabilities sourced from Yao et al (2007); these are unrelated to RAASi use. The progression of CKD patients is modelled via the decline of eGFR on a continuous scale, related to RAASi use based on Evans et al. As patients progress through the model, relevant events for each treatment arm are estimated. Event risk in CKD is related to eGFR/ CKD stage, serum potassium and RAASi use status with literature sources identified in the SLR and outcomes from the company's observational study SPARK used to provide this information. Event risk for the HF population depends on RAASi use, serum potassium levels and NYHA stage for hospitalisation. NYHA classification transition probabilities are unrelated to RAASi use. It was not possible to use the trials for these data because the trials were serum potassium based, not NYHA-based. Therefore, literature sources were identified in the SLR and selected based on containing the most relevant information. The per cycle probability of hospitalisation from HF and mortality were obtained from a range of sources, while the incident rate ratios for MACE, hospitalisation and mortality in the HF population were obtained from SPARK.

	The treatment effect of sodium zirconium cyclosilicate in reducing serum potassium is captured via a fixed effects model, which represents improvement in serum potassium levels that occur across the whole population. Each patient exhibits a unique serum potassium trajectory, reflected by patient-specific profiles which are simulated based using mixed effects regression models. These models comprise a fixed effect representing a time-varying, population-averaged mean level of serum potassium and a random effect representing patient-specific mean serum potassium levels that may be systematically higher or lower than the population-averaged mean level.
Quality of life	No health-related quality of life data were collected in the ZS-004 and ZS-005 studies; therefore, utility data were sourced from published literature. The patient's health state utility is defined as their baseline utility multiplied by their condition-specific utility, less adverse event disutility. The baseline utilities were sourced from Szende et al, utilities for HF from Göhler et al and utilities for CKD from Eriksson et al. Adverse event disutilities were taken from a range of sources.
Costs and resource use	Costs included medicine acquisition, adverse event costs and health state costs. Health state costs were further divided into CKD and HF costs, and RAASi therapy costs. Costs of underlying medical conditions (such as HF and CKD) are extrapolated beyond the trial period using a literature source aligned with the original appraisal SMC2288. The HCRU of the underlying medical conditions were sourced from Kent et al. and Ford et al. for CKD and HF disease states, respectively, and inflated to the current cost year.
PAS/contract price	There is no PAS in place for any medicine.

6.2. Results

Table 6.2 Base Case Results

Technology	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£)
SZC	£49,768	4.031	£4,954	0.462	£10,715
Standard care	£44,815	3.569	-	-	-

Abbreviations: Inc. = incremental; ICER = incremental cost-effectiveness ratio; QALYs =quality-adjusted life years; SZC = sodium zirconium cyclosilicate

6.3. Sensitivity analyses

A range of sensitivity and scenario analyses were considered, and the results of these key scenarios are provided in Table 6.3.1 below.

Table 6.3.1 Scenario Analysis Results

	Parameter	Scenario	Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
	Base case		£4,954	0.462	£10,715
1	Population split	35.70% HF, 64.30% CKD population split (Pooled ZS-004 and ZS-005 trial data)	£5,060	0.491	£10,306
2	CKD patients	CKD patients starting at stage 3a (CKD population only)	£4,005	0.338	£11,839
3	RAASi	All RAASi down-titration, up-titration and discontinuation managed in secondary care	£5,146	0.462	£11,131

4	RAASi	No RAASi discontinuation/ down-titration with serum potassium of <6.0 mmol/L in the sodium zirconium cyclosilicate arm	£13,307	1.349	£9,862
5	Dosage	Sodium zirconium cyclosilicate treatment dosage 5g daily	£3,485	0.462	£7,539
6	Mortality	No conditional mortality	£1,039	0.220	£4,713
7	Time Horizon	Time horizon: 5 years from baseline	£1,626	0.127	£12,828
8		Time horizon: 20 years from baseline	£4,909	0.457	£10,751
9		Time horizon: 16.01 years from baseline	£4,834	0.446	£10,829
10		Time horizon: 26.01 years from baseline	£4,945	0.461	£10,719
11	Disutility for hypokalaemia	Disutility for hypokalaemia: -0.004	£4,954	0.462	£10,717
12		Disutility for hypokalaemia: -0.012	£4,954	0.462	£10,721
13		Disutility for hypokalaemia: -0.019	£4,954	0.462	£10,726
14	Treatment duration	52-week treatment duration, no retreatment	£2,458	0.336	£7,312
15		52-week treatment duration, retreatment allowed	£8,496	0.635	£13,370

Abbreviations: CKD: chronic kidney disease; HF: heart failure; HK: hyperkalaemia; ICER: incremental cost-effectiveness ratio; LYG: life-year gain; QALY: quality-adjusted life-year; RAASi: renin-angiotensin-aldosterone system inhibitor; SZC: sodium zirconium cyclosilicate.

6.4. Key strengths

- The choice of comparator is standard care where no targeted therapy is administered. This is justified as there are currently no pharmacological treatments accepted for use in Scotland for this patient population. Furthermore, it is mentioned that the primary intervention in Scotland for those with persistent hyperkalaemia with serum potassium of 5.5 to 6.0 mmol/L is modification of concomitant RAASi therapy. Subsequently, patients in both arms are assumed to be eligible for this in the model, where three relevant states are included.
- All appropriate costs appear to be included. Furthermore, resource use for hyperkalaemia events and RAASi alteration costs were validated by clinical experts.

6.5. Key uncertainties

- Costs and clinical outcomes are not extrapolated beyond the study period as the longest consecutive period that any patient can be on sodium zirconium cyclosilicate in the model is 12 weeks, which the company state as reflective of UK clinical practice. However, there is evidence that a longer treatment duration may be more appropriate. Subsequently, serum potassium levels in the model may be overestimated, and treatment benefits

underestimated compared to clinical practice. The company later clarified that this input was based on UK Market Research. They also provided two scenarios with a treatment duration of 52 weeks; the scenario with no retreatment decreased the incremental cost-effectiveness ratio (ICER) by 32%, while the scenario with retreatment increased the ICER by 25%. Furthermore, the company stated that the first scenario (with no retreatment) is considered the more clinically plausible of the two scenarios. However, this scenario is still considered highly conservative in that it allows a time on treatment approximately four times longer than that observed in clinical practice.

- Although the main clinical studies (the three randomised controlled trials and SPARK) fully meet the inclusion criteria for the patient population in this economic analysis, majority of the other sources do not look at patients with hyperkalaemia. Subsequently, it is unclear how appropriate the inputs used in this economic analysis are for the given population. Nevertheless, the sensitivity analysis was rerun including the parameters for which there is functionality. Results illustrate that the top 15 drivers remain unaffected, showing these parameters are not key drivers.
- A conservative assumption was made that goes against significant literature and clinical expert opinion: despite the fact that sodium zirconium cyclosilicate would prevent the requirement for a low potassium diet, no disutilities were applied to standard care for this. Sodium zirconium cyclosilicate would prevent the requirement for a low potassium diet and, therefore, the quality of life benefits associated with sodium zirconium cyclosilicate may be underestimated in the model. The company was asked to provide a scenario with this included but they declined to do so, stating that the assumptions applied in the model still stand.

*Other data were also assessed but remain confidential.**

7. Conclusion

After considering all the available evidence, the Committee accepted sodium zirconium cyclosilicate for restricted use in NHSScotland.

8. Guidelines and Protocols

In 2024, the Kidney Disease: Improving Global Outcomes (KDIGO) organisation published 'KDIGO KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease.'[2]

In 2023, the UK Kidney Association published 'Clinical Practice Guidelines Treatment of Acute Hyperkalaemia in Adults.'[9]

9. Additional Information

9.1. Product availability date

April 2019

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per day (£)	Cost per year (£)
Sodium zirconium cyclosilicate	10g orally three times daily for up to 3 days then a maintenance dose of 5g to 10g once daily*	31 (correction phase) 5 to 10 (maintenance phase)	1,893 to 3,786 (maintenance phase)

Costs from BNF online on 21 April 2026. Costs do not take any patient access schemes into consideration.

** Titrated to maintain normal serum potassium.*

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 6,137 patients eligible for treatment with sodium zirconium cyclosilicate in year 1 and rising to 6,190 patients in year 3. The patient numbers may be underestimates based on clinical expert advice. The estimates were based on an average treatment duration of 84 days which aligns with clinical practice. Dosing regimens from key clinical trials (ZS-004 and ZS-005) were used as a conservative assumption, despite evidence suggesting that in clinical practice patients would receive the lower 5g dose during their maintenance phase of treatment. The estimated uptake rate was 9% in year 1 and 14% in year 3. This resulted in 537 patients estimated to receive treatment in year 1 rising to 882 patients in year 3.

The gross medicines budget impact was estimated to be £312,700 in year 1 rising to £513,600 in year 3. As there was no relevant comparator for sodium zirconium cyclosilicate and no medicines were assumed to be displaced, the net medicines budget impact was equivalent to the gross impact.

References

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This assessment is based on data submitted by the applicant company up to and including **12 June 2026.**

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC includes Scottish national contract prices in its decision-making. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document.

Patient Access Schemes (PAS): A PAS is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. The Patient Access Scheme Assessment Group (PASAG), established under the auspices of Public Services Delivery Scotland, reviews and advises NHS Scotland on the feasibility and acceptability on implementing proposed schemes. PASAG operates separately from SMC to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a PAS that has been considered acceptable for implementation by PASAG, a set of guidance notes on the operation of the scheme will be circulated to health boards' Area Drugs and Therapeutics Committees prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.