

sodium zirconium cyclosilicate 5g and 10g powder for oral suspension (Lokelma®)

AstraZeneca UK Ltd

10 January 2020

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

ADVICE: following a full submission

sodium zirconium cyclosilicate (Lokelma®) is not recommended for use within NHSScotland.

Indication under review: treatment of hyperkalaemia in adult patients.

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 produced normal serum potassium in a proportion of adults with hyperkalaemia.

The submitting company did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Chairman
Scottish Medicines Consortium

Indication

The treatment of hyperkalaemia in adult patients.¹

Dosing Information

The recommended starting dose of sodium zirconium cyclosilicate is 10g, administered three times a day orally as a suspension in water. Typically, normokalaemia is achieved within 24 to 48 hours. If patients are still hyperkalaemic after 48 hours of treatment, the same regimen can be continued for an additional 24 hours. If normokalaemia is not achieved after 72 hours of treatment, other treatment approaches should be considered.

When normokalaemia has been achieved, the minimal effective dose of sodium zirconium cyclosilicate to prevent recurrence of hyperkalaemia should be established. A starting dose of 5g once daily is recommended, with possible titration up to 10g once daily, or down to 5g once every other day, as needed, to maintain a normal potassium level. No more than 10g once daily should be used for maintenance therapy.

Serum potassium levels should be monitored regularly during treatment. Monitoring frequency will depend upon a variety of factors including other medications, progression of chronic kidney disease and dietary potassium intake. If severe hypokalaemia should occur, sodium zirconium cyclosilicate should be discontinued and the patient re-evaluated. Refer to summary of product characteristics (SPC) for further details.¹

Product availability date

April 2019

Summary of evidence on comparative efficacy

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.^{1,2} It is licensed for treatment of hyperkalaemia (high serum potassium) in adults¹. The submitting company proposed that it be positioned for use in adults with hyperkalaemia (defined as serum potassium ≥ 5.5 or ≥ 6.0 mmol/L depending on clinical context) who would otherwise need to down-titrate or discontinue their renin-angiotensin-aldosterone system inhibitor (RAASi) to maintain an acceptable serum potassium level (normokalaemia), and who have chronic kidney disease (CKD) stage 3b to 5 and/or heart failure (ejection fraction $< 35\%$). Two cases were presented, one in an acute urgent care setting and one in a long term non-urgent care setting. The Committee agreed to consider only the case for use in the non-urgent (outpatient) setting as this was more reflective of the suggested positioning.

Three phase III studies recruited adults with hyperkalaemia, defined as serum potassium ≥ 5.0 mmol/L in study ZS-003 and ≥ 5.1 mmol/L in studies ZS-004 and ZS-005, with an upper limit of 6.5 mmol/L in ZS-003 and in German centres in study ZS-005. Each study had an acute phase and a maintenance phase.

- Acute phase: In study ZS-003 patients were randomised to double-blind treatment with oral placebo or sodium zirconium cyclosilicate 1.25g, 2.5g, 5g, or 10g three times daily for two days. In study ZS-004 patients received open-label oral sodium zirconium cyclosilicate 10g three times daily for two days. In study ZS-005 patients received open-label oral sodium zirconium cyclosilicate 10g three times daily for one to three days until normal serum potassium (3.5 to 5.0 mmol/L) was achieved.
- Maintenance phase: In study ZS-003 patients treated with sodium zirconium cyclosilicate who achieved normal serum potassium (3.5 to 4.9 mmol/L) were re-randomised to their original dose of sodium zirconium cyclosilicate once daily or placebo, while patients in the placebo group were randomised to sodium zirconium cyclosilicate 1.25g or 2.5g once daily for 12 days. In study ZS-004 patients who achieved normal serum potassium (3.5 to 5.0 mmol/L) in the acute phase 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. In study ZS-005 patients who achieved normal serum potassium (3.5 to 5.0 mmol/L) in the acute phase then received open-label once daily sodium zirconium cyclosilicate 5g to 15g titrated regularly to maintain normal serum potassium levels over a one year period.

In all three studies efficacy was assessed in patients who had received at least one dose of study drug and had at least one post-baseline assessment during the relevant period (that is acute phase or maintenance phase).^{2,3-7}

In ZS-003 the primary outcome requested by the European Medicines Agency (EMA) in the acute phase was the proportion of patients who achieved normal serum potassium (3.5 to 4.9 mmol/L) within the initial 48 hours. This was significantly greater in the sodium zirconium cyclosilicate 10g, 5g and 2.5g groups, but not the 1.25g group, compared with placebo: 86%, 78%, 68% and 51% versus 48% ($p < 0.001$ for all three significant comparisons). The primary efficacy outcome in the 12-day maintenance phase was the cumulative number of days with normal serum potassium. This was significantly greater in patients who continued on sodium zirconium cyclosilicate compared with those re-randomised to placebo in the 10g group (10.2 days versus 8.2 days), 5g group (9.0 days versus 6.0 days) and in 2.5g group (8.6 days versus 6.2 days), but not in the 1.25g group (7.2 days versus 7.6 days).²

In ZS-004 the primary outcome was mean serum potassium during days 8 to 29 of the double-blind treatment phase. This was statistically significantly lower in the sodium zirconium cyclosilicate 10g and 5g once daily maintenance groups, compared with placebo: 4.5 mmol/L and 4.8 mmol/L versus 5.1 mmol/L, respectively. In the acute phase 66% (168/254) of patients had normal serum potassium (3.5 to 5.0 mmol/L) within 24 hours and 88% (221/251) within 48 hours.^{2,5}

In ZS-005 the primary outcome in the acute phase was the proportion of patients who achieved normal serum potassium (3.5 to 5.0 mmol/L). This was achieved in 78% (583/748) of patients within 72 hours, and in 66% (494/748) of patients in the initial 24 hours. In the maintenance phase the primary efficacy endpoint, proportion of patients maintaining normal serum potassium (defined as mean ≤ 5.1 mmol/L between months 3 and 13) was achieved by 88% (571/646) of patients.⁷ Primary outcomes and some secondary outcomes from ZS-003, ZS-004 and ZS-005 are summarised in tables 1 and 2.

Table 1: Proportion of patients with normal serum potassium at end of acute phase in ZS-003, ZS-004 and ZS-005 studies.^{2,7}

	ZS-003		ZS-004	ZS-005
	Placebo	10g TID	10g TID	10g TID
Normal serum potassium	48% (75/157)	86% (121/140)*	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. * primary outcome, $p < 0.001$ versus placebo in SZ-003; TID = three times daily.

Table 2: Primary and secondary outcomes in maintenance phase of ZS-003, ZS-004 and ZS-005 studies.²⁻⁷

	N	Normal potassium at end of treatment	Patients with mean serum potassium ≤ 5.1 mmol/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*	
Placebo	61	57% (33/58)		8.2	
SZC 5g once daily	65	75% (45/60)		9.0*	
Placebo	68	48% (32/66)		6.0	
ZS-004		Day 29	Over days 8 to 29		
SZC 10g once daily	51	81% (31/38)**	90% (45/50)*	13.9	4.5
SZC 5g once daily	45	67% (26/39)*	80% (36/45)*	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***	743	87% (383/439)	88% (571/646)		4.7

Primary outcomes in bold. SZC = sodium zirconium cyclosilicate, * $p \leq 0.001$ versus placebo, ** $p < 0.01$, ***dose titrated to maintain normal serum potassium.

There were subgroup analyses of outcomes from ZS-003, ZS-004 and ZS-005 in patients with (1) CKD, (2) heart failure and (3) on RAASi treatment. These were generally consistent with analyses in the total study populations, although there were some differences that may be related to limitations characteristic of subgroup analysis. The EMA review noted that the applicant concluded that sodium zirconium cyclosilicate reduced serum potassium and maintained normokalaemia independently of the underlying cause of hyperkalaemia, demonstrating similar efficacy in

subjects with CKD, heart failure, and diabetes mellitus, as well as in subjects receiving concomitant treatment with RAASi medication.²

Summary of evidence on comparative safety

Sodium zirconium cyclosilicate is a cation exchange compound that binds potassium cations in the gastro-intestinal tract in exchange for hydrogen and sodium cations. In clinical studies, sodium zirconium cyclosilicate has been associated with oedema-related adverse events, including fluid overload (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%).^{3,5,7}

Summary of clinical effectiveness issues

Sodium zirconium cyclosilicate is one of several cation exchange medicines for the treatment of hyperkalaemia, including calcium polystyrene sulfonate (Calcium Resonium[®]), sodium polystyrene sulfonate (Resonium A[®]) and patiomer (Veltassa[®]).⁸⁻¹⁰ SMC has advised (number 2084) that patiomer (Veltassa[®]) is not recommended for use within NHS Scotland. The submitting company proposed that sodium zirconium cyclosilicate be positioned for long-term use to prevent dose reduction or discontinuation of RAASi therapies in hyperkalaemic patients with CKD (stage 3b to 5) or heart failure.

Serum potassium levels are usually between 3.5 and 5.0 mmol/L. There is no agreed definition of hyperkalaemia. The European Resuscitation Council guidelines consider hyperkalaemia to be a serum potassium >5.5 mmol/L, with mild elevations defined as 5.5 to 5.9 mmol/L, moderate as 6.0 to 6.4 mmol/L and severe as ≥6.5 mmol/L. The level of raised serum potassium at which treatment is initiated can be influenced by clinical considerations, including co-morbidities.² The 2014 UK Renal Association clinical practice guideline on the treatment of acute hyperkalaemia in adults provided guidance on the treatment of moderate to severe hyperkalaemia (as defined above). It recommends a logical step-wise approach. The first step is to protect the heart and it recommends that intravenous calcium chloride or calcium gluconate is given to patients with hyperkalaemia in the presence of electrocardiogram (ECG) evidence of hyperkalaemia. The second step involves shifting potassium into cells and it recommends that insulin-glucose (10 units soluble insulin in 25g glucose) is used to treat severe hyperkalaemia and may be used to treat moderate hyperkalaemia.

Nebulised salbutamol (10 to 20mg) is recommended as adjuvant therapy for severe hyperkalaemia and it is suggested that it may be used as adjuvant therapy for moderate hyperkalaemia. However, salbutamol should not be used as monotherapy in the treatment of severe hyperkalaemia. The third step involves removal of potassium from the body with cation-exchange resins. It is suggested that cation-exchange resins are not used in the emergency treatment of severe hyperkalaemia, but may be considered in patients with mild to moderate hyperkalaemia.¹¹ Several other guidelines address the management of milder hyperkalaemia in non-urgent care settings. These include recommendations to discontinue or dose reduce RAASi, which may be temporary.¹²⁻

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Clinical experts consulted by SMC considered that sodium zirconium cyclosilicate fills an unmet need in this therapeutic area, namely long-term treatment of hyperkalaemia to prevent dose reduction or discontinuation of RAASi therapy. They advised that currently cation exchange resins can be used short-term to manage hyperkalaemia, but they are not usually continued in the long-term. They note that current management of patients in the proposed positioning would be to withhold RAASi. Other interventions used include dietary potassium restriction advice, treatment of metabolic acidosis with oral bicarbonate and addition of diuretics.

Across the sodium zirconium cyclosilicate studies the primary outcomes differed, although they all assessed serum potassium levels. Evidence from studies ZS-003, ZS-004 and ZS-005 indicated that sodium zirconium cyclosilicate 10g three times daily (the licensed dose for the initial treatment of hyperkalaemia) resulted in normal serum potassium levels in the majority of patients at the end of an acute phase lasting two to three days.

In ZS-003 at the end of the 12-day subacute phase patients who remained on sodium zirconium cyclosilicate had more normokalaemic days and a significantly greater proportion had normal serum potassium compared with those re-randomised to placebo. In ZS-004, mean serum potassium over days 8 to 29 was significantly lower with sodium zirconium cyclosilicate 5g and 10g daily compared with placebo. Normal serum potassium was achieved over days 85 to 365 by 88% of patients given sodium zirconium cyclosilicate titrated between 5g to 15g once daily in ZS-005.²⁻⁷

In ZS-003 there appears to have been a substantial proportion of patients (23%) who met the primary outcome, normokalaemia (serum potassium 3.5 to 5.0 mmol/L), at baseline in the acute phase, with an imbalance across the sodium zirconium cyclosilicate 10g, 5g, 2.5g, 1.25g and placebo groups: 29%, 20%, 22%, 18% and 25%, respectively. Also, there appeared to be baseline imbalances across the groups in the proportions of patients with the highest levels of potassium (5.6 to 6.5 mmol/L), 15%, 20%, 28%, 26% and 26%, and mildly elevated potassium (5.0 to 5.3 mmol/L), 66%, 57%, 51%, 49% and 60%, respectively.^{2,3}

In the maintenance phase of ZS-005 the dose of sodium zirconium cyclosilicate could be titrated above the licenced dose of 5g to 10g once daily to an unlicensed dose of 15g once daily. However, only 12% (87/746) had a dose of 15g at some point during the study and the mean and median dose were 7.18g and 5.74g, respectively, with 87% having a mean dose of 5 to <10g.⁷

Patients recruited to the studies had hyperkalaemia defined as serum potassium of ≥ 5.0 mmol/L in ZS-003 and ≥ 5.1 mmol/L in ZS-004 and ZS-005.^{2,7} Several guidelines address the management of hyperkalaemia and generally do not recommend intervention until levels exceed 5.5 mmol/L.¹²⁻¹⁶ 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.^{3,5,7} It is likely that some patients in the studies had serum potassium levels that would not require management in clinical practice. The sodium zirconium cyclosilicate SPC notes that there is limited experience in patients with serum potassium concentrations greater than 6.5 mmol/L.¹

The positioning proposed by the company is for use in patients 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. In ZS-003, ZS-004 and ZS-005 the proportions of patients receiving RAASi therapy were 67% (502/753), 70% (180/258) and 70% (527/751), respectively. It is not known how many of these patients had CKD (stage 3b to 5) and/or heart failure. However, in the respective studies substantial proportions of patients had CKD, 62% (465/753), 66% (169/258) and 68% (513/751) and heart failure, 40% (300/753), 36% (94/258) and 38% (285/751). There were no data provided for the subgroup of patients receiving RAASi therapy who had CKD and/or heart failure. However, in ZS-003, ZS-004 and ZS-005 there were subgroup analyses in patients (1) with CKD; (2) with heart failure; and (3) receiving RAASi treatment. These were generally consistent with analyses in the total study populations, although they are associated with limitations characteristic of subgroup analysis.²⁻⁷

ZS-003, ZS-004 and ZS-005 did not include patients on dialysis. The current SPC notes that sodium zirconium cyclosilicate has not been studied in patients receiving dialysis treatment. There are no posology instructions for use in dialysis.¹

The submission did not provide any evidence for use of sodium zirconium cyclosilicate in combination with insulin plus dextrose or use in an acute emergency care setting. There was no comparative data versus other cation-exchange medicines, such as calcium polystyrene sulfonate (Calcium Resonium[®]), sodium polystyrene sulfonate (Resonium A[®]), which may be used in practice after initial treatment of hyperkalaemia with insulin plus dextrose.

The one-year ZS-005 study was not placebo-controlled and there were no long-term safety or efficacy data beyond one year, which is a limitation for a medicine proposed for long-term use. There was no evidence to quantify the efficacy of sodium zirconium cyclosilicate relative to no treatment in preventing the discontinuation or reduction of RAASi. Also, there was no evidence that the benefits of RAASi on clinical outcomes would be maintained during concomitant administration of sodium zirconium cyclosilicate.

Clinical experts consulted by SMC considered that sodium zirconium is a therapeutic advance as it could allow RAASi therapy to continue in patients who would otherwise discontinue this due to hyperkalaemia. They note that its place in therapy would be for the treatment of hyperkalaemia in patients with renal disease and heart failure who would otherwise have to discontinue or reduce the dose of their RAASi therapy.

Summary of comparative health economic evidence

The submitting company provided a cost-utility analysis evaluating the use of sodium zirconium cyclosilicate against standard practice (not including other available cation exchange therapies), in a population of patients with hyperkalaemia defined as serum potassium of >5.5 or >6.0 mmol/L with CKD stage 3b–5 and/or heart failure who would otherwise need to down-titrate or discontinue their cardio-renal protective RAASi therapy to maintain a clinically acceptable serum potassium level (i.e. normokalaemia). Separate analyses were provided to represent use in the acute care and outpatient settings but as noted above, the Committee agreed to consider the use in the outpatient setting only and thus the analysis reported here relates only to this population. The choice of comparator differed depended on the severity of the hyperkalaemia, with patients in the acute care setting and/or a serum potassium level of ≥ 6.5 mmol/L receiving emergency insulin-dextrose, and the remaining patients receiving dietary intervention and modification of concomitant medications such as RAASi. Although not stated by the submitting company, the economic model assumed patients requiring renal replacement therapy would not be eligible for treatment with sodium zirconium cyclosilicate.

A patient-level, fixed-time increment, stochastic simulation was developed to model costs and consequences of sodium zirconium cyclosilicate treatment for a cohort of 60,000 individual patients over a one year time horizon in the case of acute treatment or lifetime (80 years) in the case of outpatient treatment. The model structure covered a broad range of health states relating to the underlying disease (heart failure: New York Heart Association [NYHA] I – NYHA IV; CKD: CKD3b – CKD5), treatment-related factors (RAASi changes, treatment-related adverse events and treatment initiation/discontinuation) adverse clinical outcomes (hyperkalaemic event [‘severe’ or ‘less severe’, cardiovascular events, hospitalisation) and a number of absorbing health states (background mortality, heart failure mortality, CKD mortality and receipt of renal replacement therapy [RRT]).

Patient-level serum potassium trajectories were modelled based on a mixed effects regression model, utilising data from the ZS-004 and ZS-005 studies for sodium zirconium cyclosilicate and ZS-003 study for standard practice. Serum potassium thresholds were assigned based on clinical expert input, which were assumed to result in requirement for management of a subsequent hyperkalaemic event or down-titration/discontinuation of RAASi therapy. Numerous published literature sources were required to inform relationships between parameters in the model (such as serum potassium levels or disease stage) and associated events (such as hospitalisation or mortality).

Published health state utility values were applied for the underlying condition (heart failure or CKD) and disease stage, and subsequently age-adjusted. A publication by Gohler et al 2009 reported data from a randomised controlled trial for patients with heart failure, however applied an unusual method of applying population valuation tariffs at an individual level based on the patient’s country of origin.¹⁷ This resulted in utility estimates that may not fully align with UK societal preferences. Utility data from Eriksson et al 2016 reported utility estimates for patients with chronic kidney disease, with limited information on the valuation approach.¹⁸ The range of utilities from this population (prior to age adjustment) is fairly limited (from CKD3b: 1.00 to CKD5: 0.92). An alternative approach using HUI-3 estimates was tested in scenario analysis (from CKD stage 3b: 0.85 to CKD stage 5: 0.68).¹⁹

Medicines acquisition costs were applied for sodium zirconium cyclosilicate and standard practice, where applicable. Wastage was applied for sodium zirconium cyclosilicate during the initial treatment phase. Patients receiving sodium zirconium cyclosilicate were assumed to receive treatment for up to 28 days at first hyperkalaemia episode in the outpatient setting, and a maximum of 52 weeks per episode for subsequent hyperkalaemia events. Additional resource components included inpatient stays, blood tests, outpatient visits and management of adverse events. These were generally appropriate, although limited details were provided regarding disease state-specific costs. An assumption was made that sodium zirconium cyclosilicate results in a reduced duration of inpatient stay at each admission for an acute hyperkalaemia event.

A patient access scheme was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a discount is offered on the list price of the medicine.

Two base case analyses were presented according to the underlying disease (heart disease/ CKD). Sodium zirconium cyclosilicate resulted in positive ICERs in the outpatient setting. The results are summarised in Table 3. SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish these results. As such, only the without-PAS figures can be presented.

Table 3: Base-case cost-effectiveness results (List price)

Population	Costs			QALYs			ICER
	SZC	Standard care	difference	SZC	Standard care	difference	
HF outpatient							
Base case, at list price	£28,271	£15,776	£12,495	4.044	3.511	0.534	£23,410
CKD outpatient							
Base case, at list price	£45,646	£41,543	£4,103	3.137	2.703	0.435	£9,438

Abbreviations: CKD, chronic kidney disease; HF, heart failure; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life years; SZC, sodium zirconium cyclosilicate; Δ, incremental.

An extensive range of scenario analyses were provided. The key results at the list price are presented in table 4. These highlight that the cost-effectiveness of sodium zirconium cyclosilicate in the longer-term outpatient setting is sensitive in particular to the duration of treatment, the approach to estimating clinical effectiveness of standard practice, and the assumption that reductions in serum potassium level through intervention with sodium zirconium cyclosilicate will result in improvements in adverse clinical outcomes. These sensitivities are greatest for patients with heart failure. The submitting company indicated that the use of a higher starting threshold of 6.0mmol/l reduces the influence of the sensitivities, although did not provide sufficient details to support restricted acceptance in this subpopulation.

Table 4. Summary of results from scenario analyses of SZC vs SoC, outpatient setting (list price)

Scenario	Description	ICER	
		HF	CKD
Base case		£23,410	£9,438
1.	S-K threshold for treatment and RAASi change in HF, outpatient setting: ≥ 6.0 mmol/L	£7,005	N/A
2.	Outpatient setting maximum duration of treatment: lifetime	£26,191	£14,959
3.	SoC S-K profile: data from ZS-004 placebo subgroup with baseline S-K ≥ 6.0	£18,863	£22,864
4.	Proportion of patients on RAASi therapy at baseline: 100% (based on clinical expert input)	£23,258	£10,476
5.	Alternative HSUV estimates for CKD: use of HUI-3 ¹⁷	N/A	£12,820
6.	SZC wastage assumption: Cost of a 30-sachets pack applied to each cycle in the maintenance phase (wastage of 2 sachets per cycle)	£25,009	£10,930
7.	SZC arm, "severe" HK management cost: £3,093.34 (4 inpatient days, 2 insulin-dextrose administrations; equal to SoC arm)	£23,492	£10,708
8.	Removal of RRT absorbing state for CKD patients (CKD 5 patients remain in the model until death)	N/A	£11,633
9.	Relationships between S-K and adverse clinical outcomes: strength of U-shaped relationships reduced by 50% compared to base case and the literature	£34,078	£9,231
10.	Relationships between S-K and adverse clinical outcomes: relationship removed	£103,383	£12,970

Scenario	Description	ICER	
		HF	CKD
11.	Removal of relationship between S-K and adverse clinical outcomes, plus use of S-K ≥ 6.0 mmol/L as threshold for HK episode in HF patients	£4,898	N/A

Abbreviations: HF, heart failure; HK, hyperkalaemia; HSUV, health state utility value; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; RAASi, renin-angiotensin-aldosterone system inhibitor; S-K, serum potassium; SoC, standard of care; SZC, sodium zirconium cyclosilicate, Δ , incremental. SW Quadrant: South-west quadrant: SZC is associated with lower QALY gains and a cost-saving.

There are a number of important limitations that have not been resolved through the scenario analyses provided:

- A causal relationship is assumed that reduction of serum potassium levels through intervention with sodium zirconium cyclosilicate will lead to improvements in clinical outcomes for patients. This assumes that RAASi benefits will be maintained in this subpopulation. No data are provided to support these relationships. Alternative more conservative scenarios testing this relationship highlight the sensitivity to this assumption (Table 4, Scenarios 9 and 10).
- The model relies on the use of several risk equations derived from observational datasets, introducing the risk of influence by unmeasured and unknown confounding factors. In some cases, the evidence does not demonstrate that these relationships are statistically significant and in others they do not appear to have adjusted the models for key covariates. However, more conservative approaches to modelling these relationships suggest the impact on the model results is likely to be limited.
- Uncertainty exists with the utility estimates. The model used non-standard methods for the heart failure population and may lack face validity for the CKD population. The use of a broader range of utilities for CKD (with a greater reduction in utilities for later disease stages) demonstrates the limited upwards sensitivity to these inputs (table 4 scenario 5).

As a result of these uncertainties, the economic case has not been demonstrated.

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

Summary of patient and carer involvement

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

- We received a patient group submission from Kidney Research UK, which is a registered charity.
- Kidney Research UK has received 16.5% pharmaceutical company funding in the past two years, with none from the submitting company.

- Hyperkalaemia is a hugely impactful condition that reduces the quality of life of patients with CKD. It can greatly affect patients' day-to-day lives and there is a daily struggle to maintain healthy levels when the patient is unable to monitor their potassium levels. Hospitalisation and treatment for acute hyperkalaemia on top of already intense treatment for kidney failure and possibly other conditions (such as diabetes) can culminate in great strain upon an individual's mental health and quality of life.
- Experiences of current treatments are mixed. Acute treatments although unpleasant do seem effective. However the longer term management of hyperkalaemia does not seem so effective and relies on patients maintaining strict control over their diet. If the longer term management of hyperkalaemia could be better managed by patients then this could reduce the incidents of acute hyperkalaemia needing hospital treatment, which can be distressing and detrimental to patients.
- The new medicine offers an additional treatment choice that could help reduce the symptoms of hyperkalaemia, as well as the anxiety and fear of high potassium levels. It would also give patients back some control in their lives and allow them more freedom to eat what they want and socialise with friends and family. Giving patients more control over their treatment could also reduce their risk of hospitalisation and invasive treatments which would improve their quality of life.

Additional information: guidelines and protocols

The UK Renal Association published clinical practice guidelines for the treatment of acute hyperkalaemia in adults in March 2014. This guidance uses the same European hyperkalaemia classifications as the position statement published by Think Kidneys, the Renal Association, and the British Society for Heart Failure. The guideline makes the following recommendations. Intravenous calcium chloride or calcium gluconate, at an equivalent dose (6.8mmol), is given to patients with hyperkalaemia in the presence of ECG evidence of hyperkalaemia. Insulin-glucose (10 units soluble insulin in 25g glucose) by intravenous infusion is used to treat severe (potassium ≥ 6.5 mmol/L) hyperkalaemia and may be used to treat moderate (potassium 6.0-6.4 mmol/L) hyperkalaemia. Nebulised salbutamol 10-20mg is used as adjuvant therapy for severe (potassium ≥ 6.5 mmol/L) hyperkalaemia but not as monotherapy and it may be used as adjuvant therapy for moderate (potassium 6.0 to 6.4 mmol/L) hyperkalaemia. Cation-exchange resins are not used in the emergency treatment of severe hyperkalaemia, but may be considered in patients with mild to moderate hyperkalaemia. In primary care patients with severe hyperkalaemia (potassium ≥ 6.5 mmol/L) should be referred to secondary care for immediate assessment and treatment. All patients with mild (potassium ≥ 5.5 -5.9 mmol/L) or moderate (potassium 6.0 to 6.4 mmol/L) hyperkalaemia should have a review of their medication and diet and regular monitoring of serum potassium; the urgency of assessment and frequency of potassium monitoring will depend on individual circumstances. It is recommended that renin-angiotensin drugs (ACE-inhibitors, angiotensin II receptor blockers, aliskiren), potassium sparing diuretics, and/or loop diuretics are stopped during acute illness lasting > 24 hours duration particularly when associated with hypovolaemia or hypotension (for example, sepsis, diarrhoea and/or vomiting). Also, that renal

function is assessed before commencing treatment with drugs that can cause hyperkalaemia and thereafter, renal function and serum potassium be monitored in the community after initiation, after dose adjustments and during acute illness.¹¹

In March 2016 the Scottish Intercollegiate Guidelines Network (SIGN) issued publication number 147, Management of chronic heart failure: A national clinical guideline. This guidance notes that some rise in urea, creatinine and potassium is to be expected after initiation of an ACE inhibitor; if an increase is small and asymptomatic no action is necessary. An increase in potassium up to 5.5 mmol/L and an increase in creatinine of up to 50% above baseline or 266 micromol/L are acceptable. If urea, creatinine or potassium do rise excessively consider stopping concomitant nephrotoxic drugs (for example, NSAIDs), other potassium supplements or retaining agents (triamterene, amiloride, spironolactone, eplerenone) and, if there are no signs of congestion, reducing the dose of diuretic. If greater rises in creatinine or potassium persist despite adjustment of concomitant medications, the dose of the ACE inhibitor should be halved and blood urea, creatinine and electrolytes rechecked within one to two weeks. If potassium rises to >5.5 mmol/L or creatinine increases by >100% or to above 310 micromol/l the ACE inhibitor should be stopped and specialist advice sought.¹²

A position statement entitled Changes in kidney function and serum potassium during ACEI (angiotensin converting enzyme inhibitors)/ARB (angiotensin receptor blocker)/diuretic treatment in primary care was published by Think Kidneys, the Renal Association, and the British Society for Heart Failure in October 2017. This statement identified that hyperkalaemia is common in patients with chronic kidney disease especially if patients are treated with ACEI, ARB, MRA (e.g. spironolactone), or NSAIDs. It is recommended that management in primary care depends on the severity of hyperkalaemia and on the clinical context. Hyperkalaemia is classified as follows:

- Severe hyperkalaemia = serum potassium ≥ 6.5 mmol/L
- Moderate hyperkalaemia = serum potassium 6.0 to 6.4 mmol/L
- Mild hyperkalaemia = serum potassium 5.5 to 5.9 mmol/L

The position statement recommends that patients with severe hyperkalaemia and patients with moderate and mild hyperkalaemia who are acutely unwell are referred to acute care. In clinically stable patients with moderate or mild hyperkalaemia the statement recommends that a review of medications should be undertaken. In those with moderate hyperkalaemia this would include immediately stopping any ACEI, ARB or MRA and repeating serum potassium within 1 week and in those with mild hyperkalaemia consider halving dose or one or both of any ACEI, ARB or MRA, consider halving dose of one or both. This should be followed by a review of indications. (NB patients should not be treated with combinations of ACEI and ARB). If these medicines are used for hypertension, consider an alternative antihypertensive drug. If these medicines are used for heart failure with reduced ejection fraction or kidney disease with albuminuria, re-start at a lower dose once serum potassium < 5.5 mmol/L and then continue to monitor: if the patient was on a combination of ACE or ARB and an MRA, only re-start one of these drugs at a time. If the dose has been reduced continue these medicines and monitor.¹³

The European Society of Cardiology published Guidelines for the diagnosis and treatment of acute and chronic heart failure in 2016.² These guidelines include a section on hyperkalaemia and recommends that management of acute hyperkalaemia (6.0mmol/L) may require a short-term cessation of potassium-retaining agents and RAASi, but this should be minimised and RAASi should be carefully reintroduced as soon as possible while monitoring potassium levels. The guideline noted that two new potassium binders, patiromer and sodium zirconium cyclosilicate, were under consideration for regulatory approval and initial results from patients with heart failure were available, which confirm the efficacy of these therapies in reducing serum potassium and preventing recurrent hyperkalaemia in patients with heart failure and CKD in the context of treatment with RAASi.¹⁴

In January 2015 the National Institute for Health and Care Excellence (NICE) published an updated version of Clinical Guideline 182: Chronic kidney disease in adults: assessment and management. This guidance makes the following relevant recommendations:

- Do not routinely offer a RAAS inhibitor to people with CKD if their pretreatment serum potassium concentration is greater than 5.0mmol/L.
- When hyperkalaemia precludes use of renin–angiotensin system antagonists, assessment, investigation and treatment of other factors known to promote hyperkalaemia should be undertaken and the serum potassium concentration rechecked.
- Concurrent prescription of drugs known to promote hyperkalaemia is not a contraindication to the use of renin–angiotensin system antagonists, but be aware that more frequent monitoring of serum potassium concentration may be required.
- Stop renin–angiotensin system antagonists if the serum potassium concentration increases to 6.0mmol/L or more and other drugs known to promote hyperkalaemia have been discontinued.¹⁵

The Association of British Clinical Diabetologists (ABCD) and Renal Association published clinical guidelines: Hypertension management and renin-angiotensin-aldosterone system blockade in patients with diabetes, nephropathy and/or chronic kidney disease provide some guidance on the management of potassium to allow the safe use of RAASi in patients with diabetes and CKD.¹⁶

SIGN published Diagnosis and management of chronic kidney disease: A national clinical guideline (SIGN 103) in 2008. This guidance has subsequently been archived.²⁰

Additional information: comparators

There are no established comparator medicines administered long-term to manage hyperkalaemia in patients with CKD or heart failure who are on RAASi therapy.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per day (£)
Sodium zirconium cyclosilicate	10g orally three times daily for up to 3 days then a maintenance dose of 5g to 10g once daily*	42.72 7.12 to 14.24 (maintenance dose)
Calcium polystyrene sulfonate	15g orally three to four times daily	12.32 to 16.43
Sodium polystyrene sulfonate	15g orally three to four times daily	8.04 to 10.72
Patiromer**	8.4g to 25.2g orally once daily	5.75 to 11.50

*Doses are for general comparison and do not imply therapeutic equivalence. Costs from eMC Dictionary of Medicines and Devices browser on 07 January 2020. Costs do not take any patient access schemes into consideration. *Titrated to maintain normal serum potassium. **not recommended for use by SMC*

Additional information: budget impact

Outpatient setting

The submitting company estimated the population eligible for treatment to be 141 patients in year 1 and 5,279 patients in year 5 to which confidential estimates of treatment uptake were applied. The gross and net medicines budget impact was estimated at £27k (year 1) and £5.1m (year 5) at list prices. Input from SMC clinical experts suggests that these patient numbers may represent overestimates, and the uptake rates appear to be based on an assumption.

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

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This assessment is based on data submitted by the applicant company up to and including 13 December 2019.

**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: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme 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. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards 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.