Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2288

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

AstraZeneca UK Ltd

07 August 2020

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 resubmission

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

**Indication under review:** treatment of hyperkalaemia in adult patients.

**SMC restriction:** patients with hyperkalaemia (defined as a serum potassium of >6.0mmol/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 produced normal serum potassium in a proportion of adults with hyperkalaemia.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) delivering the cost-effectiveness results upon which the decision was based, or a PAS/list price that is equivalent or lower.

**Chairman**
**Scottish Medicines Consortium**

## Indication

The treatment of hyperkalaemia in adult patients.[1]

## Dosing Information

**Correction phase**

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.

**Maintenance phase**

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 adults[1]. The submitting company has requested that SMC considers sodium zirconium cyclosilicate when positioned for use in adults with hyperkalaemia (defined as serum potassium >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) to maintain an acceptable serum potassium level (normokalaemia), which is usually <6.0mmol/L in Scottish clinical practice.

Evidence is based on three phase III studies that recruited adults with hyperkalaemia, defined as serum potassium ≥5.0 mmol/L in study ZS-003 and ≥5.1mmol/L in studies ZS-004 and ZS-005, with an upper limit of 6.5mmol/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 (higher than the maximum recommended maintenance dose of 10g daily) 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 versus placebo in the sodium zirconium cyclosilicate 10g (licensed acute phase dose), 5g and 2.5g groups, but not the 1.25g group: 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 groups, compared with placebo: 4.5 mmol/L and 4.8 mmol/L versus 5.1mmol/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 ≤5.1mmol/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 ≤5.1mmol/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* | |
| 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 |

SZC = sodium zirconium cyclosilicate. ≠ dose titrated to maintain normal serum potassium. * p≤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 studies in patients with (1) CKD, (2) heart failure and (3) on RAASi treatment. There were also post hoc subgroup analyses in patients with baseline serum potassium >6.0 mmol/L in ZS-004 and ZS-005. 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. 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%).[2,7]

## 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 patiromer (Veltassa®).[8-10] The submitting company has requested that SMC considers sodium zirconium cyclosilicate when positioned for use to prevent dose reduction or discontinuation of RAASi therapies in hyperkalaemic patients (serum potassium >6.0 mmol/L) with CKD (stage 3b to 5) and/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] 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.[11-15]

Clinical experts consulted by SMC considered that there is an unmet need in this therapeutic area, namely for a long-term treatment of hyperkalaemia that avoids 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. 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 sodium zirconium cyclosilicate 10g three times daily 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).

In ZS-003 at the end of the 12-day subacute phase patients who remained on sodium zirconium cyclosilicate, had more normokalaemic days compared with those re-randomised to placebo (primary outcome). In addition, a significantly greater proportion of patients who remained on sodium zirconium cyclosilicate had normal serum potassium levels compared to placebo. In ZS-004 the primary outcome, mean serum potassium over days 8 to 29 was significantly lower with sodium zirconium cyclosilicate 5g and 10g compared with placebo. Within patients who remained in the study at the end of treatment (day 29) normal serum potassium (3.5 to 5.0 mmol/L) was achieved by 67%, 81% versus 51% in the respective groups (secondary outcome). Another secondary outcome described normal serum potassium as a mean of ≤5.1mmol/L. This was achieved over days 8 to 29 by 80% and 90% of patients given sodium zirconium cyclosilicate 5g and 10g versus 46% given placebo in ZS-004 and it 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 (primary outcome). Also, in the latter study 87% of patients who remained in the study at the end of treatment (day 365) had normal serum potassium (≤5.1 mmol/L).[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%, 26%, 28% 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 to 15g once daily. However, only 12% (87/746) received a dose of 15g at any point during the study and the mean and median doses 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] The normal range for serum potassium is 3.5 to 5.0 mmol/L.[2] Several guidelines address the management of hyperkalaemia and generally do not recommend intervention until levels exceed 5.5 mmol/L.[11-15] 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 serum potassium >6.0mmol/L and 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, across the studies substantial proportions of patients had comorbidities of CKD (62% to 68%) and heart failure (36% to 40%). There were no data provided for the subgroup of patients receiving RAASi therapy who had CKD and/or heart failure. Only a small proportion of study patients had serum potassium > 6.0 mmol/L at baseline representing the company's proposed positioning. 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] There was no evidence that sodium zirconium cyclosilicate allowed patients to continue with RAASi therapy or improved direct health outcomes.

ZS-003, ZS-004 and ZS-005 did not include patients on dialysis. However, the SPC includes dosing instructions for patients receiving dialysis based on the DIALIZE study.[1]

There are 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 1-year ZS-005 study was not placebo-controlled and there are no long-term safety or efficacy data beyond one year, which is a limitation for a medicine proposed for long-term use. There is also no evidence of efficacy for sodium zirconium cyclosilicate in preventing the discontinuation or reduction of RAASi.

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 current standard of care (SoC), in a population of patients with hyperkalaemia defined as serum potassium of >6.0mmol/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). Analyses were carried out in the outpatient setting. The choice of comparator differed depending on the severity of the hyperkalaemia, with patients experiencing a serum potassium level of ≥6.5mmol/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 the costs and consequences of sodium zirconium cyclosilicate treatment for a cohort of 60,000 individual patients over a lifetime time horizon (80 years). 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 events ['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. However, the number of patients used to estimate these trajectories was relatively small. Serum potassium thresholds were assigned based on clinical expert input, which were assumed to result in management of hyperkalaemia through discontinuation of RAASi (comparator arm), or treatment with of SZC (intervention arm). 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.[16] 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.[17] The range of utilities from this population is fairly limited (from CKD3b: 1.00 to CKD5: 0.92). The impact of using

different sources of health state utility values for the heart failure and CKD populations was investigated in a number of scenario analyses which showed a minor impact on results.

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 in the first hyperkalaemia episode 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. An assumption was made that sodium zirconium cyclosilicate results in a reduced duration of inpatient stay at each admission for a severe 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 failure/CKD). Sodium zirconium cyclosilicate was associated with an increase in costs and quality-adjusted life-years (QALYs) versus standard care for both heart failure and CKD, resulting in positive incremental cost effectiveness ratios (ICERs). The list price results are summarised in Table 3**Error! Reference source not found.**.

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)**

| Setting | Costs | | | QALYs | | | ICER |
|---|---|---|---|---|---|---|---|
| | SZC | Standard care | Δ | SZC | Standard care | Δ | |
| **HF outpatient** | | | | | | | |
| Base case, at list price | £26,439 | £20,978 | £5,461 | 3.590 | 2.811 | 0.780 | £7,005 |
| **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; QALYs, quality-adjusted life years; SZC, sodium zirconium cyclosilicate; Δ, incremental. | | | | | | | |

An extensive range of scenario analyses were provided. The key results at list price are summarised in Table 4. These highlight that the cost-effectiveness of sodium zirconium cyclosilicate is stable relative to the base case but that results are most sensitive to the approach to estimating the clinical effectiveness of standard practice and the treatment duration of sodium zirconium cyclosilicate. These sensitivities are greatest for patients with heart failure.

**Table 4: Summary of results from scenario analyses of SZC vs SoC (list price)**

| Scenario | Description | ICER | |
|---|---|---|---|
| | | HF | CKD |
| Base case | | £7,005 | £9,438 |
| 1 | Maximum duration of treatment: lifetime | £10,423 | £14,959 |
| 2 | SoC S-K profile: data from ZS-004 placebo subgroup with baseline S-K ≥6.0 | £15,366 | £22,864 |
| 3 | Proportion of patients on RAASi therapy at baseline: 0% | £5,645 | £6,148 |
| 4 | CKD health state utility values informed by Gorodetskaya et al. 2005 | N/A | £12,820 |
| 5 | HF health state utility values informed by McMurray et al. 2017 | £6,504 | N/A |
| 6 | 10 g once daily dose is applied for all patients in the maintenance phase | £13,697 | £19,328 |
| 7 | Relationships between S-K and adverse clinical outcomes: U-shaped relationships entirely removed (100% removed) | Dominates | £12,970 |
| 8 | Statistically non-significant relationship between S-K and CV events in the CKD population for some of the S-K intervals (Luo et al. 2016) removed | N/A | £9,443 |
| 9 | Statistically non-significant relationship between S-K and hospitalisation in the CKD population (Luo et al. 2016) removed | N/A | £9,714 |
| 10 | Statistically non-significant relationship between RAASi and mortality in the CKD population (Xie et al. 2016) removed | N/A | £9,105 |
| 11 | Statistically non-significant relationship between S-K and CV events in the HF population for some of the S-K intervals (Desai et al. 2018) | £7,523 | N/A |

**Abbreviations**: HF, heart failure; HSUV; ICER, incremental cost-effectiveness ratio; RAASi, renin-angiotensin-aldosterone system inhibitor; S-K, serum potassium; SoC, standard of care; SZC, sodium zirconium cyclosilicate.

There are a number of limitations as follows:

- The number of patients used to estimate S-K trajectories for sodium zirconium cyclosilicate and standard care in the patient populations that are the subject of the resubmission is relatively small; this creates uncertainty around the generalisability of results to the wider patient population. The impact of this uncertainty on results is unclear.
- 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. Nonetheless, more conservative approaches to modelling these relationships suggest the impact on the model results is likely to be limited.

- 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. However, removal of these relationships appears to have minimal impact on results.

Despite the uncertainties noted above, the economic case has 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 an 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. 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 improved then this could reduce the incidents of acute hyperkalaemia needing hospital treatment, which can be distressing and detrimental to patients.
- Sodium zirconium cyclosilicate 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 could give patients back some control in their lives and reduce the risk of hospitalisation and invasive treatments, which would improve quality of life.

## Additional information: guidelines and protocols

The UK Renal Association published updated clinical practice guidelines for the treatment of acute hyperkalaemia in adults in June 2020. 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 relevant recommendations. In primary care, patients with severe hyperkalaemia (potassium ≥6.5mmol/L) are admitted to hospital for immediate assessment and treatment. Calcium polystyrene sulfonate is not used in the emergency treatment of severe hyperkalaemia, but may be considered in patients with

moderate hyperkalaemia. Sodium zirconium cyclosilicate is initiated in secondary care only. Sodium zirconium cyclosilicate is recommended, and patiromer is suggested, as an option for the emergency management of acute life-threatening hyperkalaemia. Sodium zirconium cyclosilicate or patiromer is recommended as an option for the outpatient management of persistent hyperkalaemia (serum potassium ≥6.0mmol/L) in patients with stage 3b to 5 CKD or heart failure receiving a suboptimal dose of RAAS inhibitor (or also not receiving RAAS inhibitors due to hyperkalaemia in the case of patiromer). RAAS inhibitors should be stopped in patients with serum potassium ≥6.0mmol/L who do not meet the criteria for sodium zirconium cyclosilicate or patiromer. In patients with mild hyperkalaemia (potassium ≥5.5-5.9mmol/L), increased monitoring is recommended along with consideration of dose reductions of RAAS inhibitors. It is recommended that RAAS inhibitors are used with caution if serum potassium is >5.0mmol/L and are withheld during acute illness (for example sepsis, hypovolaemia and/or acute kidney injury) at all severities of hyperkalaemia.[18]

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 266micromol/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 >5.5mmol/L or creatinine increases by >100% or to above 310micromol/l the ACE inhibitor should be stopped and specialist advice sought.[11]

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, mineralocorticoid receptor antagonists (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 ≥6.5mmol/L
- Moderate hyperkalaemia = serum potassium 6.0 to 6.4mmol/L
- Mild hyperkalaemia = serum potassium 5.5 to 5.9mmol/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 <5.5mmol/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.[12]

The European Society of Cardiology published Guidelines for the diagnosis and treatment of acute and chronic heart failure in 2016. 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.[13]

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.[14]

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]

## 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.

## Additional information: 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* | **42.72 (correction phase)**<br><br>**7.12 to 14.24 (maintenance dose)** | <br><br>**2,592 to 5,183 (maintenance dose)** |

*Costs from dm+d on 22 June 2020. Costs do not take any patient access schemes into consideration. *Titrated to maintain normal serum potassium.*

## Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 2,815 patients eligible for treatment with sodium zirconium cyclosilicate in year 1 and 13,199 patients eligible for treatment in year 5.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*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 28 July 2020.

**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.*