NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Sodium zirconium cyclosilicate for the treatment of persistent hyperkalaemia with a serum potassium level between 5.5 mmol/litre and 5.9 mmol/litre

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using sodium zirconium cyclosilicate in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: October 2025

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using sodium zirconium cyclosilicate in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 26 November 2025
- Second evaluation committee meeting: 14 January 2026
- Details of the evaluation committee are given in section 4

1 Recommendations

1.1 Sodium zirconium cyclosilicate should not be used to treat hyperkalaemia in adults when:

- it is persistent and
- serum potassium levels are between 5.5 mmol/litre and 5.9 mmol/litre.

1.2 This recommendation is not intended to affect treatment with sodium zirconium cyclosilicate that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop.

What this means in practice

Sodium zirconium cyclosilicate is not required to be funded and should not be used routinely in the NHS in England for the condition and population in the recommendations.

This is because there is not enough evidence to determine whether sodium zirconium cyclosilicate is value for money in this population.

Why the committee made these recommendations

For people with persistent hyperkalaemia and chronic kidney disease or heart failure, NICE technology appraisal guidance 599 recommends sodium zirconium cyclosilicate (a potassium binder), if they have a serum potassium level of at least 6.0 mmol/litre. This evaluation reviews the evidence for sodium zirconium cyclosilicate for persistent hyperkalaemia when serum potassium levels are between 5.5 mmol/litre and 5.9 mmol/litre. For this population, the company has provided new evidence since the last evaluation.

Standard care for persistent hyperkalaemia with a serum potassium level between 5.5 mmol/litre and 5.9 mmol/litre is:

- dietary changes to maintain normal potassium levels and
- changes to current medicines such as renin–angiotensin–aldosterone system (RAAS) inhibitors, which are commonly used to treat chronic kidney disease and heart failure.

Evidence suggests that people who have sodium zirconium cyclosilicate are less likely to have to reduce their RAAS inhibitor dosage than people on standard care. But it is unclear whether this is because sodium zirconium cyclosilicate lowers potassium levels or whether it has an additional impact independent of this.

There are uncertainties in the economic model. This is because of some of the assumptions it uses, including how:

- sodium zirconium cyclosilicate affects RAAS inhibitor treatment
- serum potassium levels are linked to adverse outcomes.

Because of the uncertainties in the clinical evidence and economic modelling, it is not possible to determine the most likely cost-effectiveness estimates for sodium zirconium cyclosilicate.

So, sodium zirconium cyclosilicate should not be used to treat persistent hyperkalaemia in adults with a potassium level between 5.5 mmol/litre and 5.9 mmol/litre.

2 Information about Sodium zirconium cyclosilicate

Marketing authorisation indication

2.1 Sodium zirconium cyclosilicate (Lokelma, AstraZeneca) is indicated for ‘the treatment of hyperkalaemia in adult patients’.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for sodium zirconium cyclosilicate.

Price

2.3 The list price of sodium zirconium cyclosilicate is £10.40 per 10-g sachet or £5.20 per 5-g sachet (BNF, October 2025)

2.4 Costs may vary in different settings because of negotiated procurement discounts.

Carbon Reduction Plan

2.5 Information on the Carbon Reduction Plan for UK carbon emissions for AstraZeneca will be included here when guidance is published.

3 Committee discussion

The evaluation committee considered evidence submitted by AstraZeneca, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

3.1 Hyperkalaemia is a high level of potassium in the blood. The company's clinical trials recruited people with serum potassium levels above 5.0 mmol/litre. Clinical experts highlighted that people with chronic kidney disease and heart failure are at increased risk of hyperkalaemia. They added that renin–angiotensin–aldosterone system (RAAS) inhibitors are commonly used to manage chronic kidney disease and heart failure. These can include angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs) and aldosterone receptor antagonists. But, RAAS inhibitors can also increase serum potassium levels. Persistent hyperkalaemia generally refers to a persistently elevated serum potassium level that is of clinical significance. People with persistent hyperkalaemia and chronic kidney disease or heart failure may

not be able to have optimal RAAS inhibitor treatment. The committee understood that for people with persistent hyperkalaemia and chronic kidney disease or heart failure, a key aim of treatment is to maintain RAAS inhibitor treatment and ideally facilitate an optimised dosage.

Clinical management

Treatment pathway and comparator

3.2 The aim of treating persistent hyperkalaemia is to lower serum potassium levels to prevent acute life-threatening hyperkalaemia. The NICE technology appraisal guidance on sodium zirconium cyclosilicate for treating hyperkalaemia (from here TA599) and NICE technology appraisal guidance on patiromer for treating hyperkalaemia recommend sodium zirconium cyclosilicate and patiromer, which are potassium binders, for persistent hyperkalaemia with a serum potassium level of 6.0 mmol/litre or more. The company stated there are limited treatment options for people with persistent hyperkalaemia with a serum potassium level of 5.5 mmol/litre to 5.9 mmol/litre. NICE's guideline on chronic kidney disease: assessment and management recommends:

- not routinely offering a RAAS inhibitor to adults with chronic kidney disease if their pretreatment serum potassium is more than 5.0 mmol/litre and
- stopping RAAS inhibitor treatment if the serum potassium level increases to 6.0 mmol/litre or more and other medicines known to promote hyperkalaemia have been stopped.

Clinical advice to the company stated that for people with serum potassium of 5.5 mmol/litre to 5.9 mmol/litre, in the absence of potassium binders, healthcare professionals would start down titrating RAAS inhibitors. So, the company stated that the appropriate comparator was standard care. This included lifestyle changes to maintain normal potassium levels and down titrating or stopping of

RAAS inhibitors. The clinical experts at the committee meeting agreed. The committee concluded that standard care, which included down titrating or stopping RAAS inhibitors, was the appropriate comparator.

Uncertainties in the evidence and modelling of TA599

3.3 In its submission, the company intends to expand the population to people with a serum potassium level of 5.5 mmol/litre to 5.9 mmol/litre. It also aims to address the uncertainties in the evidence and modelling identified during the appraisal of TA599. These included:

- absence of evidence on sodium zirconium cyclosilicate's treatment effect on clinical outcomes, such as mortality and major adverse cardiovascular events (MACE), based on the ZS-003, ZS-004 and ZS-005 studies (clinical trials for sodium zirconium cyclosilicate)
- uncertainties in the association between reducing serum potassium levels and improved outcomes such as reduced mortality and MACE and
- uncertainties in sodium zirconium cyclosilicate's effect on stopping, down titrating or restarting RAAS inhibitor treatment.

Evidence addressing the uncertainties identified in TA599

3.4 To address the evidence gaps and uncertainties in TA599, the company did a systematic literature review. The review assessed the efficacy and safety of sodium zirconium cyclosilicate in people with persistent hyperkalaemia with a serum potassium of 5.0 mmol/litre or more. It also did another systematic literature review to identify evidence demonstrating the relationship between RAAS inhibitor dosage and long-term clinical outcomes. It also presented data from 2 real-world studies; SPARK and the ZORA study reanalysis.

The company did not identify any additional evidence from clinical trials showing sodium zirconium cyclosilicate's treatment effect on clinical outcomes such as overall survival and health-related quality of life. The

EAG noted there is also a lack of evidence on how down titrating or stopping RAAS inhibitor treatment affects serum potassium in people with chronic kidney disease or heart failure.

SPARK study

3.5 The SPARK study was a UK-specific, retrospective observational longitudinal study done using data from the Clinical Practice Research Datalink and linked datasets. A key aim of SPARK was to investigate the relationship between serum potassium levels and hospitalisation, MACE and mortality. To do this, the company ran multivariable regression models, which were stratified by variables of interest to account for confounding variables. A generalised estimating equations model was used to estimate adjusted incidence rate ratios for hospitalisation, MACE and mortality for people with 5.5 mmol/litre to 5.9 mmol/litre versus 4.5 mmol/litre to 4.9 mmol/litre. The company presented results separately for chronic kidney disease and heart failure. In both groups, the results showed a 'U-shaped' association between serum potassium levels and adverse outcomes, despite the adjustment of multiple confounders. That is, adverse outcomes were higher with both higher and lower serum potassium levels, compared with the 4.5 mmol/litre to 4.9 mmol/litre reference group. The company added that this should provide reassurance that this association is not due to any unidentified confounder. It added that RAAS inhibitor dosage was also adjusted for in the analysis. The exact results are considered confidential by the company and cannot be reported here. The EAG said that the SPARK study provided evidence of the risk of adverse outcomes for a single serum potassium reading. But, it did not show decreasing serum potassium levels over time caused the reduction in risk of adverse outcomes. This is because the company did not provide data on how long people spent in each serum potassium group. This data would be needed to understand the relationship between persistent hyperkalaemia and adverse outcomes. During the committee meeting, the company explained that about two-thirds of people had a second reading in

SPARK. For these people, serum potassium levels were updated dynamically in the generalised estimating equations model. But the EAG noted this was not explained in the company submission or in the clarification response. The EAG noted a study by James et al. (2021), which was identified by the company's systematic literature review but excluded from its submission. It provided information on time spent in different serum potassium level groups and adverse outcomes. Results from James et al. suggest a lower mortality risk for people spending more time with serum potassium of 5.0 mmol/litre or more compared with those spending no time in hyperkalaemia. The company stated that this finding may have been attributable to more proactive management. It added that the difference between SPARK findings and those of James et al. likely arises from differences in the dataset exposure definitions, confounding, and statistical modelling. The EAG stated that James et al. shows that the relationship between persistent hyperkalaemia and adverse outcomes is complicated. A clinical expert stated that some of the findings from James et al. complement findings from SPARK. For example, people with chronic kidney disease who spent longer with serum potassium of 5.5 mmol/litre or more had higher risk of all-cause mortality or MACE (combined outcome) than people with no time spent with hyperkalaemia. The clinical experts also stated that the correlation between elevated serum potassium and adverse outcomes is well established. But the extent to which this is caused specifically by serum potassium levels or by the subsequent down titration of RAAS inhibitors is less certain. Another clinical expert also noted findings from Rossignol et al. (2020). This study used long-term registry data to assess the interplay between hyperkalaemia and RAAS inhibitor use and their association with all-cause or cardiovascular death in people with chronic heart failure. Findings suggested that for people with heart failure, hyperkalaemia was associated with mortality. But, when adjusting for stopping RAAS inhibitor treatment, hyperkalaemia was no longer associated with mortality. The authors stated that this suggested hyperkalaemia may be a risk marker for

stopping RAAS inhibitor treatment rather than a risk factor for worse outcomes. The committee noted that the evidence discussed suggested a correlation between hyperkalaemia and adverse outcomes. But, it also noted the interplay between hyperkalaemia, stopping or down titrating RAAS inhibitor treatment and adverse outcomes. It noted that in the SPARK study, of those who had more than 1 serum potassium reading, a high proportion (exact proportion considered confidential by the company) had a reading that fell below their baseline serum potassium group at least once. Overall, the committee noted that there is likely a correlation between serum potassium levels and adverse outcomes but this does not mean that there is a causal effect. It understood that RAAS inhibitor use was adjusted for in the company's analysis. But this does not provide evidence showing that lowering serum potassium reduces the risk of adverse outcomes independent of RAAS inhibitor use. It concluded that there may be a relationship between hyperkalaemia and adverse outcomes mediated by reductions in RAAS inhibitor use. But there is substantial uncertainty whether there is a causal effect between hyperkalaemia and adverse outcomes that is independent of RAAS inhibitor use.

ZORA reanalysis study

3.6 ZORA was an observational, cohort study examining the odds of maintained RAAS inhibitor treatment at 6 months in people having sodium zirconium cyclosilicate compared with no potassium binder. The study used data from Japanese, Spanish and US health registers and hospital medical records. Primary analysis results have been published (Rastogi et al. 2024). The ZORA study reanalysis was an ad-hoc reanalysis of the Japanese and US data (permission was not given to use the Spanish data) stratified by serum potassium group. The company used propensity score matching to achieve balance (accounting for potential confounders) between the sodium zirconium cyclosilicate cohort and the no potassium binder cohort. The analysis used 33 matching variables, which were identified through subject matter knowledge. The EAG stated that

matching resulted in well-matched treatment arms. The company considered that the ZORA reanalysis results showed that, across serum potassium groups, sodium zirconium cyclosilicate helps maintain recommended RAAS inhibitor dosage after a hyperkalaemia event. The exact results are considered confidential by the company and cannot be reported here. But, the EAG considered that evidence was uncertain because the analysis used serum potassium levels at baseline only without accounting for change in serum potassium groups over time. The committee noted the limitation in the evidence. It concluded that sodium zirconium cyclosilicate treatment was likely associated with a reduced likelihood of down titrating or stopping RAAS inhibitor treatment, although the evidence was uncertain. It also had concerns with how the ZORA study reanalysis was used in the economic model (see section 3.10).

Generalisability of the ZORA study reanalysis

3.7 The EAG noted that differences in UK, Japanese and US patient baseline characteristics may affect the generalisability of the ZORA study reanalysis results to the NHS population. It added that research has shown that average potassium consumption in the Japanese population is lower than in Western countries. Additionally, in Rastogi et al. (ZORA study), meta-analysed RAAS inhibitor treatment post-index date data compared with pre-index date data showed that I^2, the most common measure of study statistical heterogeneity, was often high. This suggested heterogeneity of effect across Japan, the US and Spain in relation to stopping or changing the dosage of RAAS inhibitors. So, the EAG stated that this added further uncertainty about the generalisability of the ZORA study reanalysis results to the NHS population. During the committee meeting, the company explained that the ZORA study reanalysis results were similar between Japan and the US. Noting the ethnic differences between these 2 countries, the company suggested that there is no reason to believe the results would be different for the UK. It also noted that the baseline characteristics reported in ZORA appear broadly consistent with the clinical profiles of people having treatment in NHS

practice. A clinical expert added that the guidelines for the management of persistent hyperkalaemia in the US and Japan would be similar to the UK. When comparing the ZORA study reanalysis population and the NHS population, the committee noted similarity in the guidelines followed and in baseline characteristics. But, it also noted the EAG's concerns about differences in potassium consumption between the Japanese population and Western countries. The committee concluded that the ZORA study reanalysis results are broadly generalisable to the NHS population.

Economic model

Model structure

3.8 The company modelled the cost effectiveness of sodium zirconium cyclosilicate using the same model structure used in TA599. Specifically, a patient-level fixed-time increment simulation model. In the model, disease progression in people with heart failure is represented by transitions between New York Heart Association classes 1 to 4. For people with chronic kidney disease, progression is represented by a continuous decline in the estimated glomerular filtration rate. Transitions through chronic kidney disease stages are tracked until the onset of end-stage renal disease and the start of renal replacement therapy (RRT). Relevant clinical events, such as a hyperkalaemia event, and adverse outcomes are also incorporated into the model. The committee concluded that the model structure was acceptable for decision making.

Relationship between serum potassium and adverse outcomes

3.9 In the model, the risk of adverse outcomes (MACE, hospitalisation and mortality) is dependent on the serum potassium level (amongst other factors). Overall, the EAG thought that the SPARK study does not provide robust evidence to confirm the association between persistent hyperkalaemia and adverse outcomes (see section 3.5). It provided a scenario in which the serum potassium level was assumed to have no effect on the risk of MACE, hospitalisations and mortality (serum

potassium group incidence rate ratios set to equal 1). This had a small impact when applied to the company base case. The committee recalled its discussion on the likely correlation between serum potassium levels and adverse outcomes, and the extent to which this correlation may be mediated by RAAS inhibitor use alone (see section 3.5). It understood that the minor impact of removing this association may be because, in the model, people on sodium zirconium cyclosilicate are more likely to maintain optimal RAAS inhibitor treatment. So, they then have fewer adverse outcomes. But in the standard care arm, serum potassium levels are mainly reduced by adjusting RAAS inhibitor treatment. So, in the model the impact of serum potassium levels on adverse outcomes such as mortality is smaller than the impact of RAAS inhibitor mediation. The committee understood that RAAS inhibitor use mediated by sodium zirconium cyclosilicate treatment is the main driver of the adverse outcomes in the model (see section 3.10). It concluded that the company's approach of modelling the correlation between serum potassium level and adverse outcomes may be acceptable for decision making, but there are uncertainties. The committee would welcome additional information or evidence justifying that correlation, independent of RAAS inhibitor use.

Impact of sodium zirconium cyclosilicate on RAAS inhibitor use

3.10 The company derived the probability of down titrating or stopping RAAS inhibitor treatment from the ZORA study reanalysis. The probabilities were dependent on the treatment arm and on the serum potassium level. The EAG highlighted that this means that people with the same serum potassium level will have different probabilities of down titrating or stopping RAAS inhibitor treatment depending on whether they are on sodium zirconium cyclosilicate or standard care. Sodium zirconium cyclosilicate treatment affects the probabilities of stopping or down titrating RAAS inhibitors in 2 ways:

- directly, due to having sodium zirconium cyclosilicate and

- indirectly, through changes in serum potassium level.

The committee noted this may have double counted the benefits of sodium zirconium cyclosilicate treatment in the model. The company stated that this assumption was supported by the ZORA study reanalysis results. But the EAG noted that only baseline serum potassium levels were used in the ZORA study reanalysis and no adjustment was made to account for changes in serum potassium levels during the follow-up period. So, the results do not support the company's assumption that sodium zirconium cyclosilicate impacts the probability of stopping or down titrating RASS inhibitor treatment independent of serum potassium levels. The EAG thought that the different probabilities of stopping or down titrating RAAS inhibitor treatment for people on sodium zirconium cyclosilicate and people on standard care is likely to have been captured by the decrease in serum potassium after starting treatment. So, in its base case, for each serum potassium level, the EAG assumed that the probability of stopping or down titrating RAAS inhibitor treatment was the same for both arms. It presented 2 base cases: one with the probabilities derived from the sodium zirconium cyclosilicate arm, and the other with probabilities derived from the standard care arm. During the committee meeting, the clinical experts explained that the different probabilities of stopping or down titrating RAAS inhibitor treatment between the sodium zirconium cyclosilicate and standard care arms could be caused by healthcare-professional behaviour. Specifically, for a given serum potassium level, healthcare professionals may feel more comfortable maintaining RAAS inhibitor treatment if someone is having a potassium binder. The EAG stated this was speculative and not supported by evidence. It reiterated that that the difference in the proportion of people stopping or down titrating RAAS inhibitors between treatment arms could be a result of sodium zirconium cyclosilicate lowering serum potassium levels. This in turn would reduce the likelihood of stopping or down titrating RAAS

inhibitor treatment. The committee recalled its discussion on the correlation between hyperkalaemia and adverse outcomes. Specifically that hyperkalaemia may be a risk factor for stopping RAAS inhibitor treatment, rather than a risk factor for worse outcomes. This is because of the likely interplay between hyperkalaemia, stopping RAAS inhibitor treatment, and adverse outcomes (see section 3.5). It understood that RAAS inhibitor use mediated by sodium zirconium cyclosilicate treatment is the main mechanism for the modelling of adverse outcomes (see section 3.9).

The committee acknowledged that to some extent the differences in probabilities of stopping or down titrating RAAS inhibitor treatment between the 2 arms may be explained by healthcare-professional behaviour. But, it was not convinced by the large differences as modelled. It considered the EAG's approach but noted that it still did not account for changes in in serum potassium levels over time. It concluded that there is uncertainty in the company's modelling of sodium zirconium cyclosilicate's impact on RAAS inhibitor use. It would like to see supporting evidence that justifies the differential stopping or down titration of RAAS inhibitor treatment between the 2 arms. It also requested an analysis estimating sodium zirconium cyclosilicate's impact on RAAS inhibitor use over time using RAAS inhibitor stopping or down-titration rates per time-unit in each serum potassium category. This is instead of using serum potassium category at baseline and accounts for people switching categories over time. In this way, discrete time probabilities for stopping or down titrating RAAS inhibitor treatment conditional on current serum potassium level could also be assessed.

Sodium zirconium cyclosilicate treatment duration

3.11 The company assumed that everyone still having sodium zirconium cyclosilicate at 12 weeks stops treatment, then restarts for 12 weeks if their serum potassium is 5.5 mmol/litre or more. The company stated that

this assumption was based on clinical expert opinion and market research. The EAG noted that in the company's advisory board report, only 1 healthcare professional (of 5 consulted by the company) expressed a view consistent with a short treatment duration. It added that for the market research data, there was no information on:

- whether people were having sodium zirconium cyclosilicate for acute or persistent hyperkalaemia
- their serum potassium level when treatment was started and
- why treatment with sodium zirconium cyclosilicate was stopped.

Clinical advice to the EAG was that while dosage reduction may occur in clinical practice, most people would not stop treatment with sodium zirconium cyclosilicate. This is because stopping treatment would be expected to increase serum potassium to the level before sodium zirconium cyclosilicate treatment started. During the committee meeting, clinical experts stated that the duration of treatment for sodium zirconium cyclosilicate should be individualised. Short-term treatment may be appropriate to treat an acute event of hyperkalaemia for some people. But for some people, when the underlying cause of hyperkalaemia was not reversible, lifelong treatment would be appropriate. The committee recalled that the company's submission focuses specifically on the population with persistent hyperkalaemia and chronic kidney disease or heart failure. It noted that for people with hyperkalaemia caused by these conditions, the cause is likely not reversible. So, stopping sodium zirconium cyclosilicate after 12 weeks would likely result in increased serum potassium levels. The committee thought that if it accepted the company's assumption of stopping after 12 weeks, a stopping rule would need to be included if sodium zirconium cyclosilicate was recommended. The clinical experts stated that this was inappropriate because if a person's serum potassium level is controlled by sodium zirconium cyclosilicate, stopping treatment could cause a return to persistent hyperkalaemia. The committee

acknowledged that some people may stop for reasons such as adverse events, and noted that this was captured in an annual stopping rate within the economic model. The committee concluded that assuming a lifelong treatment duration for sodium zirconium cyclosilicate (subject to an annual stopping rate) is appropriate for decision making.

Impact of stopping sodium zirconium cyclosilicate treatment

3.12 For the sodium zirconium cyclosilicate arm, the company assumed the probability of stopping or down titrating RAAS inhibitor treatment is the same for people taking sodium zirconium cyclosilicate and those who have stopped. The company stated that this approach was justified because treatment-arm data from the ZORA study reanalysis included people who started sodium zirconium cyclosilicate but then stopped before the end of the follow-up period. So, this data implicitly captures the impact of stopping sodium zirconium cyclosilicate on RAAS inhibitor stopping rates for a given serum potassium level. The EAG highlighted that the minimum sodium zirconium cyclosilicate treatment duration in the ZORA study reanalysis (assuming all people stopped after 120 days of treatment) expressed relative to the length of follow up (180 days) is 66.7%. It stated that the company base case average sodium zirconium cyclosilicate treatment duration is 2.3 years. As a proportion of expected survival in years, this is 28.3% (2.3 years out of an expected 8.1 years of survival). So, the EAG thought that applying sodium zirconium cyclosilicate probabilities from the ZORA study reanalysis to all people initially taking sodium zirconium cyclosilicate is likely to overestimate its benefit on RAAS inhibitor use. It noted in its preferred base case, which assumes a lifetime sodium zirconium cyclosilicate treatment duration (see section 3.11), the mean treatment duration expressed as a proportion of expected survival is approximately 70%. It stated this is more consistent with the minimum possible treatment duration in the ZORA study reanalysis expressed relative to the length of follow up (66.7%). The committee recalled its preference of assuming a lifetime treatment duration for sodium zirconium cyclosilicate (see section 3.11). It noted that

this addresses the EAG's concerns about the company's assumptions on the probabilities of stopping or down titrating RAAS inhibitor treatment applying to people who have stopped sodium zirconium cyclosilicate. So, it accepted the company's base-case assumption that the probability of stopping or down titrating RAAS inhibitor treatment is the same for people who have stopped sodium zirconium cyclosilicate as for those who are still taking it.

Sodium zirconium cyclosilicate treatment in standard care arm

3.13 In the model, people on standard care did not have a potassium binder (such as sodium zirconium cyclosilicate), even if their serum potassium level was above 6.0 mmol/litre. The company stated that this assumption was likely to have a minimal impact on model outcomes since a serum potassium level of 6.0 mmol/litre or more was unlikely. This is because it assumed that the average serum potassium level stays constant over time. It stated that this assumption was supported by the REVOLUTIONIZE I study. In that study, serum potassium levels were generally similar in recurrent and initial hyperkalaemia events. The EAG noted that the REVOLUTIONIZE I study follow up was only 6 months but the model uses a lifetime time horizon. It stated that for people on standard care, average serum potassium levels are likely to increase over time as the underlying disease progresses. It noted that the impact on cost-effectiveness results is uncertain. This is because it is not known how many people on standard care are expected to have a potassium binder over the time horizon of the model. Clinical experts stated that it would generally be expected that the serum potassium levels would increase over time. The company stated that it does not have the data needed to estimate this increase over time. But, it said that the assumption that the average serum potassium level stays constant over time in the standard care arm is conservative. This is because if an increase in serum potassium over time was modelled in the standard care arm, it would have worse outcomes relative to the sodium zirconium cyclosilicate arm. The committee thought this assumption may not necessarily be conservative if

people in the standard care arm had sodium zirconium cyclosilicate when their serum potassium levels were above 6.0 mmol/litre (in line with TA599). This is because while the standard care arm would incur extra costs, it would also receive benefit from sodium zirconium cyclosilicate. It concluded that this omission added uncertainty to the cost-effectiveness analysis, and would prefer an analysis that reflects NHS practice. So, it preferred to assume that people in the standard care arm had sodium zirconium cyclosilicate if their serum potassium levels was 6.0 mmol/litre or more. It requested that the company update its model to include this analysis. If not possible, it requested a scenario in which the maximum serum potassium level in the model is capped at 6.0 mmol/litre, to understand the impact on the cost-effectiveness results.

RAAS inhibitor model algorithm

3.14 At model entry, all people are assumed to be having optimal RAAS inhibitor dosage (that is, they are in the 'max' RAAS inhibitor state). The EAG noted that people on a suboptimal RAAS inhibitor dosage are also eligible for sodium zirconium cyclosilicate (as per TA599). The company stated that its approach was conservative because, at baseline, a higher proportion of people having standard care may have already down titrated their RAAS inhibitor dosage (compared with people having sodium zirconium cyclosilicate). But, the EAG noted that in a cost-effectiveness analysis, patient baseline values should be the same for all treatments. It stated that if the model included a proportion of people having a suboptimal RAAS inhibitor dosage at baseline, the time spent in the 'max' RAAS inhibitor state would likely decrease in both treatment arms. The extent of the decrease and impact on cost-effectiveness results may depend on the probability of up-titration in the model. The committee noted that in clinical practice, sodium zirconium cyclosilicate would be offered both to people on an optimal RAAS inhibitor dosage (who would have to down titrate or stop without sodium zirconium cyclosilicate), and to people on a suboptimal RAAS inhibitor dosage. So, the committee considered that the model does not reflect clinical practice with regards to

the baseline RAAS inhibitor dosage and adds uncertainty to the cost-effectiveness estimates. But it acknowledged that estimating the proportion of people who, in clinical practice, would start sodium zirconium cyclosilicate treatment while on a suboptimal or an optimal RAAS inhibitor dosage, would also be associated with uncertainty. So, it concluded that the company's base-case assumption, that at model entry all people are on an optimal RAAS inhibitor dosage, is acceptable for decision making.

In the model, after stopping RAAS inhibitor treatment, people may restart RAAS inhibitor treatment. The company assumed that when people restart RAAS inhibitor treatment, they return to the optimal RAAS inhibitor dosage. It added that there is a lack of data on people restarting RAAS inhibitor treatment and the dosage they would have. The EAG received clinical advice that in clinical practice people would start at a suboptimal dosage and up-titrate over time. The company stated that this was a conservative approach since people on standard care were likely to restart RAAS inhibitor treatment more cautiously (that is, at a lower dosage) than people on sodium zirconium cyclosilicate. But it acknowledged that given the lack of data, it is not known whether the speed of up-titration is impacted by whether a person is having sodium zirconium cyclosilicate. The EAG stated that because of the company's assumption, the proportion of people and the length of time spent in the 'max' RAAS inhibitor state is likely to be overestimated. It added that the impact on cost-effectiveness results may depend on the probability of up-titration of RAAS inhibitor in the model. The committee agreed that in clinical practice most people would likely restart RAAS inhibitor treatment at a suboptimal dosage and then titrate up over time. It noted the model does not reflect clinical practice with regards to the RAAS inhibitor dosage when restarting treatment. But, it acknowledged there is a lack of data on people restarting RAAS inhibitor treatment, so any assumptions about the dosages people would have on restarting would also be associated with uncertainty. So, the committee accepted that the company's base-case

assumption, that when people restart RAAS inhibitor treatment they return to the optimal dosage, is acceptable for decision making.

Chronic kidney disease health state costs

3.15 The company sourced annual costs for each chronic kidney disease stage from Kent et al. (2015). It stated that it used these costs because they were accepted in 2 recent NICE appraisals in chronic kidney disease:

- NICE technology appraisal guidance on dapagliflozin for treating chronic kidney disease
- NICE technology appraisal guidance on targeted-release budesonide for treating primary IgA nephropathy.

The EAG highlighted that in Kent et al. the costs are reported by chronic kidney disease stage at baseline. By the end of the study period, 28% of people with chronic kidney disease stage 4 and 79% of people with chronic kidney disease stage 5 at baseline had RRT. As people exit the model when they start RRT, the EAG thought that Kent et al. overestimates the cost associated with chronic kidney disease progression. So, in its base case it preferred to use chronic kidney disease health state costs from the NICE clinical guideline on chronic kidney disease in adults: assessment and management (from here CG182; now withdrawn). The company stated that information about the costs used in CG182 are no longer in the public domain, so it could not check details about how the costs were derived. It clarified that it used the CG182 costs to populate chronic kidney disease health state costs in TA599 because it was unable to identify alternative costs at the time of that evaluation. But it thought that the costs lacked face validity because there would be a significant rise in costs when a person progresses from stage 3b chronic kidney disease to stage 4. It added that a person who has stage 3b chronic kidney disease would likely be reviewed annually, but a person with stage 4 chronic kidney disease would need a review 3 times a year. There would also likely be

additional hospitalisation costs. A clinical expert confirmed that costs would increase as a person progresses to stage 4 chronic kidney disease because of increased healthcare resource use. The committee thought that there were issues with both sources of chronic kidney disease health state costs. It noted that the CG182 costs were associated with uncertainty because they did not vary across chronic kidney disease stages 3a to 4. But it was unclear whether this was because of a lack of granularity in the data or because of the data's underlying validity. It concluded that it preferred costs for chronic kidney disease stages 3a and 3b from Kent et al. because these are more up to date. But, it noted that the Kent et al. costs for stage 4 and 5 were unsuitable because they included the cost of RRT. It requested that the company remove the RRT costs from Kent et al., if the data allows. If not possible, it requested that the company explores other suitable sources (including NHS reference costs) to populate health state costs for chronic kidney disease. These should not include RRT costs.

Cost-effectiveness estimates

Company and EAG cost-effectiveness estimates

3.16 Results were provided separately for the chronic kidney disease population and heart failure population, and also for a mixed population. For the mixed population analysis, based on the SPARK study distribution, the cohort was stratified by the conditions. In the company's base-case analysis, the deterministic incremental cost-effectiveness ratios (ICERs) for sodium zirconium cyclosilicate were £16,833 per quality-adjusted life year (QALY) gained in the chronic kidney disease population and £9,053 per QALY gained in the heart failure population. For sodium zirconium cyclosilicate in the mixed population, the deterministic ICER was £12,495 per QALY gained and the probabilistic ICERs was £12,417 per QALY.

The EAG provided 2 exploratory base cases. In both, the probabilities of

stopping or down titrating RAAS inhibitor treatment for each serum potassium group were assumed to be the same between treatment arms. In 'EAG base case 1', the probabilities were based on sodium zirconium cyclosilicate values and in 'EAG base case 2' the probabilities were based on standard care values. The committee concluded that further analyses were needed to determine the most plausible estimates for decision making (see section 3.19).

Acceptable ICER

3.17 NICE's manual on health technology evaluations notes that, above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee noted the high level of uncertainty, specifically about:

- the correlation between serum potassium levels and the risk of adverse outcomes, and the extent to which the relationship is independent of RAAS inhibitor use (see section 3.5 and section 3.9)
- the assumption that sodium zirconium cyclosilicate impacts the probability of stopping or down titrating RAAS inhibitor treatment independent of serum potassium levels (see section 3.10)
- the omission of treatment with sodium zirconium cyclosilicate in the standard care arm for serum potassium levels above 6.0 mmol/litre (see section 3.13)
- the assumption that all people are on an optimal RAAS inhibitor dosage at model entry (see section 3.14)
- the assumption that when people restart RAAS inhibitor treatment, they return to the optimal dosage (see section 3.14)
- the stage 4 and stage 5 chronic kidney disease health state costs (see section 3.15).

The committee's preferences

3.18 For the cost-effectiveness analysis, the committee's preferred assumptions are:

- A lifelong treatment duration for sodium zirconium cyclosilicate (subject to an annual stopping rate; see section 3.11).
- The same probabilities of stopping or down titrating RAAS inhibitor treatment for people who have stopped sodium zirconium cyclosilicate as for those who are still having it (see section 3.12).
- People in the standard care arm go on to have sodium zirconium cyclosilicate if their serum potassium level is 6.0 mmol/litre or more. If not possible, a scenario in which the maximum serum potassium level in the model is capped at 6.0 mmol/litre (see section 3.13).
- All people are on an optimal RAAS inhibitor dosage at model entry (see section 3.14).
- When people restart RAAS inhibitor treatment, they return to the optimal dosage (see section 3.14).

The committee's requests for additional analyses

3.19 The committee could not determine the most plausible ICER without further analyses. The committee requested the following:

- Additional information or evidence justifying the correlation between serum potassium levels and risk of adverse outcomes, independent of RAAS inhibitor use (see section 3.9)
- Evidence that justifies the differential stopping or down titration of RAAS inhibitor treatment between the 2 arms; and an analysis of the rates of stopping or down titrating RAAS inhibitor treatment per time-unit spent in each serum potassium category, rather than per baseline serum potassium category (accounting for individuals switching categories over time; see section 3.10).
- Updated model functionality to include an analysis in which people in the standard care arm take sodium zirconium cyclosilicate if their serum

potassium level is 6.0 mmol/litre or more. If not possible, a scenario in which the maximum serum potassium level in the model is capped at 6.0 mmol/litre (see section 3.13).

- Removal of RRT costs from the Kent et al. (2015) estimates for chronic kidney disease stage 4 and 5. If not possible, exploration of other suitable sources (including NHS reference costs) to populate health state costs for chronic kidney disease that does not include RRT costs (see section 3.15).

Other factors

Equality

3.20 The company stated it was unable to provide economic modelling for people having long-term dialysis. It stated this was because of the paucity of data for this population on which to base economic modelling. Evidence for the safety and efficacy of sodium zirconium cyclosilicate as a treatment for pre-dialysis hyperkalaemia comes from the DIALIZE study, but the length of follow up was only 10 weeks. The company stated that about two-thirds of people having dialysis experience an episode of hyperkalaemia with a serum potassium level 5.5 mmol/litre or more each month after the interdialytic interval. So, it stated this is a population of high unmet need. It added that sodium zirconium cyclosilicate was previously incorporated into the NICE COVID-19 rapid guideline: dialysis service delivery (from here NG160; now withdrawn). It stated that restricting access to sodium zirconium cyclosilicate in this population after previously allowing access in NG160 would result in inequitable access across the full population in the marketing authorisation. Clinical advice to the EAG was that in NHS clinical practice, people with persistent hyperkalaemia who require dialysis, are not generally prescribed potassium binders. This is because dialysis effectively removes excess potassium. The company clarified that it would like the committee to consider a recommendation for sodium zirconium cyclosilicate in an emergency setting. This would apply to people on dialysis who develop

hyperkalaemia but are not able to have or access dialysis treatment. The committee noted that the population of interest for the current evaluation is people with persistent hyperkalaemia and a serum potassium level of 5.5 mmol/litre to 5.9 mmol/litre. In the NHS, this group are usually seen in a primary care or outpatient setting and are distinct from those seen in emergency settings. The committee was aware that the population with persistent hyperkalaemia who need dialysis were also included in the scope, but the committee had not seen any clinical and cost-effectiveness evidence for this population. The committee acknowledged there is an unmet need for people having dialysis in the emergency setting. But it noted that the current evaluation is for the treatment of persistent hyperkalaemia, and not for hyperkalaemia in an emergency setting. So, it concluded that the exclusion of the dialysis population was not an equality issue that it could address.

Uncaptured benefits

3.21 The company stated that there are several benefits of sodium zirconium cyclosilicate that may not be captured in the QALY calculation, including:

- The potential increased use of sodium–glucose cotransporter-2 (SGLT-2) inhibitors. SGLT-2 inhibitors can be prescribed to people with chronic kidney disease or heart failure to lower the risk of adverse outcomes. A retrospective analysis looked at 44 people with heart failure with reduced ejection fraction with a history of hyperkalaemia. It found that SGLT-2 inhibitor use increased from 66% to 84% after sodium zirconium cyclosilicate was prescribed. The company stated that data on the use of SGLT-2 inhibitors was not captured in the clinical trials and was not included in the economic model.
- The benefit of sodium zirconium cyclosilicate for people with concomitant chronic kidney disease and heart failure. The company stated that for these people, there would likely be a greater need for optimised RAAS inhibitor use. So, the company considered that

modelling populations with either chronic kidney disease or heart failure may be conservative.

- The absence of disutilities applied to standard care for a low potassium diet. The company stated that a low potassium diet impacts quality of life negatively and sodium zirconium cyclosilicate would prevent the need for a low potassium diet.

Given the uncertainties in the evidence and modelling, the committee concluded that it was uncertain whether any of these potential benefits have been captured in the model.

Conclusion

3.22 The committee agreed that further information was needed before it could decide on all its preferred modelling assumptions and understand the full impact of the uncertainties. So, it was unable to establish that sodium zirconium cyclosilicate was a cost-effective use of NHS resources. It concluded that sodium zirconium cyclosilicate should not be used to treat hyperkalaemia in adults with serum potassium level of level of 5.5 mmol/litre to 5.9 mmol/litre.

4 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee B.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Charles Crawley

Chair, technology appraisal committee B

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser, a project manager and an associate director.

Dilan Savani

Technical lead

Yelan Guo

Technical adviser

Jeremy Powell

Project manager

Emily Crowe

Associate director

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