NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final draft guidance

Sodium zirconium cyclosilicate for treating persistent hyperkalaemia

This guidance is a partial review of technology appraisal 599. TA599 recommends sodium zirconium cyclosilicate in emergency care for acute life-threatening hyperkalaemia alongside standard care. TA599 also recommends sodium zirconium cyclosilicate for people with chronic kidney disease stage 3b to 5 or heart failure if they have persistent hyperkalaemia with serum potassium levels of 6.0 mmol per litre or above and are not taking an optimised dose of RAAS inhibitors because of hyperkalaemia, and are not on dialysis. This partial review specifically considers whether to recommend sodium zirconium cyclosilicate for people with persistent hyperkalaemia with serum potassium levels of 5.5 mmol per litre and over. Following the resolution of any appeals on the final draft guidance for this partial review, TA599 will be replaced by this guidance.

1 Recommendations

1.1 Sodium zirconium cyclosilicate can be used as an option for treating hyperkalaemia in adults only if used:

- in emergency care for acute life-threatening hyperkalaemia alongside standard care or
- for persistent hyperkalaemia in people with chronic kidney disease stage 3b to 5 or heart failure, if they:

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- have confirmed serum potassium level of at least 5.5 mmol per litre and
- because of hyperkalaemia, are not taking an optimised dosage of renin-angiotensin aldosterone system (RAAS) inhibitor and
- are not on dialysis.

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 must be funded in the NHS in England for the condition and the population in the recommendations, if it is considered the most suitable treatment option. Sodium zirconium cyclosilicate must be funded in England within 90 days of final publication of this guidance.

There is enough evidence to show that sodium zirconium cyclosilicate provides benefits and value for money, so it can be used routinely across the NHS in this population.

Why the committee made these recommendations

This evaluation is a partial review of NICE technology appraisal guidance on sodium zirconium cyclosilicate for treating hyperkalaemia (TA599). This partial review assesses evidence for sodium zirconium cyclosilicate for persistent hyperkalaemia with serum potassium levels of 5.5 mmol per litre and over. See the committee papers for TA599 for full details of the evidence for serum potassium levels of 6.0mmol per litre and over.

Usual treatment for persistent hyperkalaemia with a serum potassium level between 5.5 mmol per litre and up to 6.0 mmol per litre is:

- dietary changes to maintain normal potassium levels, and
- reducing the dosage of medicines being taken for chronic kidney disease or heart failure, such as RAAS inhibitors.

Clinical-trial evidence suggests that people having sodium zirconium cyclosilicate are less likely to have to reduce their RAAS inhibitor dosage than people making dietary changes alone. The evidence also suggests that sodium zirconium cyclosilicate may lower the chance of adverse outcomes such as hospitalisation, major adverse cardiac events and death.

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

- sodium zirconium cyclosilicate affects RAAS inhibitor dosage beyond its effect on lowering sodium levels
- serum potassium levels are linked to adverse outcomes directly and indirectly, because of the likelihood that RAAS inhibitor dose will be reduced when serum potassium levels are high.

But the most likely cost-effectiveness estimate is within the range that NICE considers an acceptable use of NHS resources. So, sodium zirconium cyclosilicate can be used.

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 (excluding VAT; BNF online accessed October 2025).

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

Sustainability

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

This evaluation is a partial review of NICE's technology appraisal guidance on sodium zirconium cyclosilicate for treating hyperkalaemia (TA599). It focuses only on persistent hyperkalaemia with serum potassium levels of 5.5 mmol per litre and over. Considerations for people in emergency care for acute life-threatening hyperkalaemia, or for people with persistent hyperkalaemia with serum potassium levels of 6.0 mmol per litre or above who are not taking an optimised dose of RAAS inhibitors because of hyperkalaemia and are not on dialysis are still available in the committee papers for TA599.

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 per litre. The clinical experts explained that people with chronic kidney disease and heart failure are at increased risk of hyperkalaemia. Renin–angiotensin–aldosterone system (RAAS) inhibitors are commonly used to manage chronic kidney disease and heart failure. These include

angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and aldosterone receptor antagonists. But RAAS inhibitors can 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 at 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. NICE's technology appraisal guidance on sodium zirconium cyclosilicate for treating hyperkalaemia (TA599) and on patiromer for treating hyperkalaemia (TA623) recommend sodium zirconium cyclosilicate and patiromer, which are potassium binders, for persistent hyperkalaemia with a serum potassium level of 6.0 mmol per 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 per litre to up to 6.0 mmol per 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 per litre, and
- stopping RAAS inhibitor treatment if the serum potassium level increases to 6.0 mmol per 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 per litre to up to 6.0 mmol per 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 dietary changes to maintain normal potassium levels and down-titrating or stopping 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.

Potential impact of sodium zirconium cyclosilicate on the care pathway

3.3 The patient expert stated that there may not be clear symptoms of hyperkalaemia between 5.5 mmol per litre and up to 6.0 mmol per litre and GPs have difficulty knowing how often to test potassium levels. This can be worrying for patients. The patient expert also described delays in potassium testing. They noted that some people are advised to attend A&E because of this uncertainty. A clinical expert noted that sodium zirconium cyclosilicate may reduce the need for monitoring, support management of persistent hyperkalaemia in primary care and lower the likelihood of secondary-care admissions. They explained that although sodium zirconium cyclosilicate contains sodium, which may cause oedema in some people with severe heart failure, this can be managed with appropriate care and is not expected to cause harm. The committee concluded that access to sodium zirconium cyclosilicate may simplify the treatment and monitoring of persistent hyperkalaemia and support management in primary care. It agreed to take this into account in its decision making.

At consultation, stakeholders noted that introducing sodium zirconium cyclosilicate could reduce the need for secondary care. At the second committee meeting, a clinical expert explained that potassium binders can rapidly stabilise severe heart failure, releasing capacity from secondary to primary care. They added that they would expect clinicians in primary care

to prefer managing someone with stable heart failure on a binder, rather than someone with recurrent hyperkalaemia and worsening symptoms, which could improve management and benefit people in the long term. The clinical expert explained that maintaining optimal RAAS inhibitor therapy slows chronic kidney disease progression and that reducing or stopping treatment increases mortality risk. They noted that GPs are generally willing to manage people on sodium zirconium cyclosilicate when a clear plan is in place, and that once people are normokalaemic and optimised on RAAS inhibitors, no extra monitoring is needed. They explained that unstable potassium levels lead to frequent tests and GP visits. They advised that access to sodium zirconium cyclosilicate in primary care would support RAAS inhibitor optimisation, reduce the need for repeated monitoring, and increase clinicians' confidence. The committee acknowledged that these effects could not be quantified and decided that potential reductions in secondary care use and costs should be recognised as uncaptured benefits (see section 3.23 and section 3.24). It concluded that it would take this into account in its decision making.

Uncertainties in the evidence and modelling of TA599

3.4 In its submission, the company expanded the population to people with a serum potassium level of 5.5 mmol per litre to less than 6.0 mmol per litre (from here referred to as 5.5 mmol per litre to up to 6.0mmol per litre). It also aimed to address the uncertainties in the evidence and modelling identified during the appraisal of TA599, which included:

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

Evidence addressing the uncertainties identified in TA599

3.5 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 level of 5.0 mmol per litre or more. It did another systematic literature review to identify evidence demonstrating the relationship between RAAS inhibitor dosage and long-term clinical outcomes. It presented data from 2 real-world studies: the SPARK study and a reanalysis of the ZORA study. The company did not identify any additional evidence from clinical trials showing sodium zirconium cyclosilicate's 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

3.6 SPARK was a UK 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 the adverse outcomes of hospitalisation, MACE and mortality. To do this, the company ran multivariable regression models that 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 serum potassium levels of 5.5 mmol per litre up to 6.0 mmol per litre, compared with 4.5 mmol per litre to 4.9 mmol per litre. The company presented results separately for chronic kidney disease and heart failure. In both populations 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 per litre to 4.9 mmol per litre reference group. The company stated that this should provide reassurance that this association is not because of any unidentified confounder. The EAG said that SPARK provided evidence of the risk of adverse outcomes for a single serum potassium reading. But it did not show that 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 first committee meeting, the company explained that about two-thirds of people had a second potassium measurement 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 per litre or more compared with those spending no time in hyperkalaemia. The company stated that this finding may have been attributable to more proactive clinical 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 per 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 (see section 3.10). The committee noted that in SPARK, of those who had more than 1 serum potassium reading, a high proportion (the exact proportion is considered confidential by the company) had a reading that fell below their baseline serum potassium level at least once. The committee acknowledged there is likely a correlation between serum potassium levels and adverse outcomes, but this does not mean that there is a causal effect. At the second committee meeting and in response to consultation, the company emphasised that the James et al. study was not well designed to answer the decision problem. This was because it was designed to primarily assess long term serum potassium variability and time spent in specific serum potassium groups rather than the relationship between serum potassium and adverse outcomes. The company also assessed the relationship between adverse outcomes and elevated serum potassium levels above 5.0 mmol per litre rather than the narrower population being considered in this appraisal that is people with persistent serum potassium levels between 5.5 mmol per litre and up to 6.0 mmol per litre. The EAG maintained its opinion that SPARK does not provide robust evidence to confirm the association between persistent hyperkalaemia and adverse outcomes and preferred James et al. The committee noted the uncertainty in outcomes for persistent hyperkalaemia because of the study's design. It acknowledged that it had not been provided with a model based on James et al, so it could not base its decision on that evidence. The committee also noted that SPARK had a larger dataset. It concluded that it was acceptable to use SPARK to inform the modelling of adverse outcomes associated with serum potassium between 5.5 mmol per litre and 6.0 mmol per litre.

ZORA reanalysis

3.7 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. It 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 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 stated 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 advised that the results were uncertain because the reanalysis used serum potassium levels at baseline only, without accounting for change in serum potassium groups over time. The committee noted this limitation in the evidence, which meant that the ZORA reanalysis informed a person's chance of down-titrating or stopping RAAS inhibitors based on their serum potassium at the point hyperkalaemia was measured, but could not capture how the risk of down-titrating would change with treatment of hyperkalaemia. It had concerns about how the ZORA reanalysis was used in the economic model (see section 3.11). But it concluded that sodium zirconium cyclosilicate was likely associated with a reduced likelihood of down-titrating or stopping RAAS inhibitor treatment.

Generalisability of the ZORA reanalysis

3.8 The EAG noted that differences in UK, Japanese and US patient baseline characteristics may affect the generalisability of the ZORA reanalysis results to the NHS population. It explained that research has shown that average potassium consumption in the Japanese population is lower than the UK or US. Also, in Rastogi et al. (ZORA), 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 reanalysis results to the NHS population. During the committee meeting, the company explained that the ZORA 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 explained that the guidelines for management of persistent hyperkalaemia in the US and Japan would be similar to the UK. When comparing the ZORA 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 the UK and US. The committee concluded that the ZORA reanalysis results are broadly generalisable to the NHS population.

Economic model

Model structure

3.9 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

3.10 The company's model estimated the risk of adverse outcomes based on serum potassium levels, using data from SPARK and also, separately, based on RAAS inhibitor dose. The doses of RAAS inhibitors were modelled to be dependent on serum potassium levels. So, higher serum potassium was modelled to have both a direct effect on adverse outcomes independent of RAAS inhibitor use and an independent effect because of decreased RAAS inhibitor dose. At the first committee meeting, a clinical expert noted that a long-term registry study, Rossignol et al. (2020), showed 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 understood that RAAS inhibitor use was adjusted for in the company's analysis of SPARK, but noted that this did not provide evidence that lowering serum potassium reduces the risk of adverse outcomes independent of RAAS inhibitor use. The committee noted this was highly relevant because the company modelled the risk of adverse outcomes associated with RAAS inhibitor down-titration and serum potassium levels separately in the model.

The EAG provided a scenario in which the serum potassium level was assumed to have no effect on the risk of MACE, hospitalisations or mortality (serum potassium group incidence rate ratios set to equal 1). This had a small impact when applied to the company's base case. The committee understood that the minor impact of removing this association may be because, in the model, people having 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. At the first committee meeting, the committee understood that RAAS inhibitor use mediated by sodium zirconium cyclosilicate treatment is the main driver of the adverse outcomes in the model. 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 welcomed additional information or evidence justifying that correlation, independent of RAAS inhibitor use.

At consultation, to support its assertion that the effect of RAAS inhibitor use had been accounted for in its analysis of SPARK, the company recalled the e-values it had calculated in its original submission, to quantify the strength of the unmeasured confounder needed to reverse the observed relationship between serum potassium and adverse outcomes. The company reiterated that the results showed that an unmeasured confounder would need to be highly correlated with the clinical outcome and imbalanced between serum potassium groups to reverse or nullify the correlation between serum potassium and adverse outcomes seen in SPARK. At the second committee meeting, the committee noted that optimised RAAS inhibitor dose was the key, potentially unmeasured, confounder. The company explained it would be

extremely difficult to capture optimised RAAS inhibitor use in real-world evidence because dosage is individualised. A clinical expert explained that hyperkalaemia is an independent risk factor for fatal cardiac arrhythmias, which often leads to down-titration or stopping of RAAS inhibitors because of reduced clinician confidence. The committee noted that serum potassium levels of over 6.0 mmol per litre are considered a risk factor for fatal cardiac arrhythmia, and clinicians may also down titrate at lower serum potassium levels. The clinical experts had concerns that the impact of persistent hyperkalaemia within the 5.5 mmol per litre up to 6.0 mmol per litre range means that clinicians may be reluctant to start RAAS inhibitors and are likely to down-titrate them, if potassium binders are not available. The committee accepted that some independent effect of serum potassium on adverse outcomes was plausible. It acknowledged the extent of this effect based on the analysis in SPARK was highly uncertain (see section 3.6). But it concluded that it would accept the company's approach of modelling the correlation between serum potassium level and adverse outcomes as an independent effect to the impact of RAAS inhibitor down-titration.

Impact of sodium zirconium cyclosilicate on RAAS inhibitor use

3.11 The company derived the probability of down-titrating or stopping RAAS inhibitor treatment from the ZORA reanalysis. The probabilities were dependent on the treatment arm and the serum potassium level. The EAG explained 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 having sodium zirconium cyclosilicate or standard care. So, sodium zirconium cyclosilicate treatment was modelled to affect the probabilities of stopping or down-titrating RAAS inhibitors in 2 ways:

- directly, from having sodium zirconium cyclosilicate
- indirectly, from 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 reanalysis results. But the EAG noted that only baseline serum potassium levels were used in the ZORA reanalysis and no adjustment was made to account for changes in serum potassium levels during the follow-up period (see section 3.7). So, the results do not support the company's assumption that sodium zirconium cyclosilicate impacts the probability of stopping or down-titrating RAAS inhibitor treatment independent of serum potassium levels. The EAG advised that the different probabilities of stopping or down-titrating RAAS inhibitor treatment for people having sodium zirconium cyclosilicate or 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 of ZORA, and the other with probabilities derived from the standard care arm of ZORA. 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 professionals' 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.

At the first committee meeting, the committee acknowledged that the differences in probabilities of stopping or down-titrating RAAS inhibitor treatment between the 2 arms may be partly explained by healthcare professionals' behaviour. But it was not convinced by the large differences as modelled. 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 company's differential stopping or down-titration of RAAS inhibitor treatment between the 2 arms for people with the same serum potassium levels. 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.

At consultation, the company stated that 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 was not possible with the available data. The company presented data from the CONTINUITY trial to support differential RAAS inhibitor use, dependent on whether a person had sodium zirconium cyclosilicate rather than no potassium binder. This trial included adults admitted to hospital with serum potassium levels from 5.0 mmol per litre to 6.5 mmol per litre who had not had sodium zirconium cyclosilicate at admission. At discharge, people were randomised to continue sodium zirconium cyclosilicate or have no potassium binder. Clinicians, aware of allocation, made decisions about RAAS inhibitor optimisation at discharge. The results showed that more

people were prescribed RAAS inhibitor therapy directly following treatment with sodium zirconium cyclosilicate for a hyperkalaemic event compared with standard care (the exact estimates are confidential and cannot be reported here). The EAG questioned whether CONTINUITY supports using different probabilities of RAAS inhibitor down-titration or stopping for people with persistent hyperkalaemia who are already using RAAS inhibitors. It noted that differences in RAAS inhibitor use between the CONTINUITY cohorts were much smaller than those seen in the ZORA cohorts. The company disagreed with the EAG's view stating that the size of the difference was similar across ZORA and CONTINUITY.

At the second committee meeting, the company clarified that it is implausible for 2 people with the same serum potassium level having sodium zirconium cyclosilicate or standard of care to have the same rate of RAAS inhibitor optimisation. This is because, for people having standard of care, serum potassium is controlled by down-titrating or stopping RAAS inhibitor therapy. But for people having sodium zirconium cyclosilicate, potassium is controlled by the binder, allowing RAAS inhibitor therapy to continue. The company noted that this relationship applies across all serum potassium stratifications. The clinical expert explained that it is plausible that down-titration rates would differ if sodium zirconium cyclosilicate were available, because both actions (starting sodium zirconium cyclosilicate and stopping RAAS inhibitors) would not need to happen at the same time.

The committee agreed with the company and clinical expert that it was plausible that the chance of down-titrating RAAS inhibitors would differ at the point of treatment initiation with sodium zirconium cyclosilicate compared with standard care. It did not consider down-titration rates would differ for someone with persistent hyperkalaemia on the maximum dose of sodium zirconium cyclosilicate compared with

someone not on it. The clinical experts explained that for someone taking sodium zirconium cyclosilicate, clinicians aim to maintain RAAS inhibitors, particularly in severe heart failure when these medicines are lifesaving. They explained that if the sodium zirconium cyclosilicate dose is low, it could be increased to control potassium levels to support RAAS inhibitor optimisation. The clinical expert stated that sodium zirconium cyclosilicate usually restores normokalaemia within 2 to 3 days. So, it would be rare to need further RAAS inhibitor down-titration if a person was having the maximum dose of sodium zirconium cyclosilicate. But if further RAAS inhibitor down-titration were needed, management would be similar for people having sodium zirconium cyclosilicate or standard of care.

Beyond the initial treatment period, the committee expected that clinical decisions to reduce RAAS inhibitors based on serum potassium levels would be similar in each modelled treatment arm. The committee noted that the ZORA reanalysis had limitations because it estimated the chance of down titrating RAAS inhibitors based on baseline serum potassium, rather than serum potassium levels over time. So, it discussed the plausible probabilities of down-titration given the estimates based on the 2 arms of the ZORA reanalysis. The clinical experts (who see people in secondary care) and a GP member of the committee explained that confidence in maintaining RAAS inhibitor therapy differs between primary and secondary care. The committee considered what would happen in primary care, because this is where ongoing decisions for persistent hyperkalaemia treated with sodium zirconium cyclosilicate would be expected to happen. A clinical expert explained that GPs would likely have less confidence to maintain RAAS inhibitors if a person had persistent hyperkalaemia. They noted that such cases would usually trigger requests for advice and guidance or referral to secondary care. The clinical experts expect clinicians' confidence in maintaining RAAS inhibitors in people with serum

potassium levels between 5.5 mmol per litre up to 6.0 mmol per litre would increase over time if sodium zirconium cyclosilicate were available for this population.

The committee decided that the standard-of-care arm in ZORA was more reflective of primary care practice. So, it requested a scenario in which the model uses differential rates by treatment arm using the rates from the ZORA reanalysis for the first 3 model cycles (12 weeks) and then uses the EAG's approach of a single rate by treatment arm for the rest of the model duration, using standard-of-care estimates from ZORA. The company provided this scenario after the committee meeting.

Sodium zirconium cyclosilicate treatment duration

3.12 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 per 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, the 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. But for some people, when the underlying cause of hyperkalaemia was not reversible, lifelong treatment would be needed. 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 noted that if it accepted the company's assumption of stopping after 12 weeks, a stopping rule should be considered if sodium zirconium cyclosilicate were 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 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.

At consultation, the company stated it disagreed with the EAG's assumption that a lifetime sodium zirconium cyclosilicate treatment duration was appropriate because the modelled treatment duration using this assumption does not reflect the treatment duration observed in clinical practice. The company explained that its modelling approach of 12 weeks of treatment followed by reinitiation if needed reflected observed treatment durations for sodium zirconium cyclosilicate in its currently recommended indication. In support of this it presented patient episode statistics (PES) data for sodium zirconium cyclosilicate

prescriptions in primary care in England over the past 6 years. Over 36 months, the proportions of people on treatment in the PES analysis and the company's base case dropped sharply within the first 4 months. In the PES data set this was mostly in the first 2 months but in the company's model this was at 3 months (in accordance with the modelled stopping rule). From month 6, both curves showed a similar proportion of people on treatment. The company noted the EAG's base-case curve showed consistently higher proportions of people on treatment than the PES data. The EAG noted that it was unclear from the PES data why so many people stopped treatment early in follow-up. The clinical expert noted this may be because some people in the PES cohort had sodium zirconium cyclosilicate for treatment of acute episodes, but PES prescribing would be after hospital discharge from secondary care when the acute episode is resolved. The clinical expert noted that GPs may be more likely to stop sodium zirconium cyclosilicate if hyperkalaemia is resolved. But in secondary care, clinicians may be more likely to maintain sodium zirconium cyclosilicate to achieve the optimal RAAS inhibitor dose. The clinical experts also noted that it was difficult to interpret how the PES data from people with severe hyperkalaemia related to milder hyperkalaemia because treatment decisions may differ in this group. The company did not challenge the assumption of a lifetime treatment and noted that the duration of treatment is likely to fall somewhere between the company and EAGs estimates of treatment duration. The committee concluded that the EAG's approach of 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

3.13 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 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 explained that the minimum sodium zirconium cyclosilicate treatment duration in the ZORA 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's 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 advised that applying sodium zirconium cyclosilicate probabilities from the ZORA 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 3.12), the mean treatment duration expressed as a proportion of expected survival is about 70%. It stated this is more consistent with the minimum possible treatment duration in the ZORA reanalysis expressed relative to the length of follow up (66.7%). The committee noted its preference of assuming a lifetime treatment duration for sodium zirconium cyclosilicate (see section 3.12). 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 in the standard care arm

3.14 In the model, people having standard care did not have a potassium binder (such as sodium zirconium cyclosilicate), even if their serum potassium level was above 6.0 mmol per 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 per 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 which serum potassium levels were generally similar in recurrent and initial hyperkalaemia events. The EAG noted that the REVOLUTIONIZE I follow-up period 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. The 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. At the first committee meeting, 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 per 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 it 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 level was 6.0 mmol per 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 per litre, to understand the impact on the cost-effectiveness results.

In response to consultation, the company provided a scenario in its updated model in which people in the standard care arm started treatment and had retreatment for a 12--week treatment cycle (consistent with the sodium zirconium cyclosilicate arm), but with a treatment threshold of serum potassium 6.0 mmol per litre rather than 5.5 mmol per litre. The company noted that the modelled sodium zirconium cyclosilicate arm remains consistent with the original model submitted. At the second committee meeting, the EAG noted that the company's updated model assumes a small proportion of people in the standard care arm would reach potassium levels above 6.0 mmol per litre. The clinical expert explained that if RAAS inhibitor therapy is reduced or stopped, potassium levels may fall initially, which would lower the immediate risk of hyperkalaemia. But in end-stage chronic kidney disease or heart failure the risk of cardiovascular events and recurrent hyperkalaemia would increase over time. The company noted that a very small proportion of people in the analysis had serum potassium levels above 6.0 mmol per litre, which was reflected in the small decrease in the incremental cost-effectiveness ratio (ICER). The committee acknowledged that the ICER decreased when sodium zirconium cyclosilicate was introduced in the standard-of-care arm for serum potassium levels of 6.0 mmol per litre or more and this was an area of uncertainty but noted the ICER impact was minimal. It concluded that it preferred the company's updated scenario in which people in the standard care arm started treatment with sodium zirconium cyclosilicate if serum potassium was 6.0 mmol per litre or more, because this was more reflective of clinical practice.

RAAS inhibitor model algorithm

3.15 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 in TA599). 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 decided 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 because people on standard care were likely to restart RAAS inhibitor treatment more cautiously (that is, at a lower dosage) than people having 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 the 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 up-titrate 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.

Chronic kidney disease health state costs

3.16 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 evaluations for chronic kidney disease:

- dapagliflozin for treating chronic kidney disease (TA1075) and
- targeted-release budesonide for treating primary IgA nephropathy (TA937).

The EAG noted 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. Because 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 NICE's clinical guideline on chronic

kidney disease in adults (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. At the first committee meeting, 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. At consultation, the company provided a scenario in which the chronic kidney disease health state costs from Kent et al had been recalculated with the exclusion of dialysis and transplant costs. The EAG advised the company's updated approach was reasonable and included this in

its updated base cases. The committee concluded that the company's scenario with updated chronic kidney disease health state costs was acceptable.

Probability of up-titration

3.17 In the model, the company assumed a 49.7% probability of returning to the maximum RAAS inhibitor state for people having sodium zirconium cyclosilicate or standard care, using the value from TA599 sourced from the Luo study (2016). The company noted that the ZORA reanalysis was not appropriate for estimating the probability of up-titration because it is not known how many people up-titrated to an optimal RAAS inhibitor dose or restarted RAAS inhibitor therapy after stopping. The EAG preferred to use the ZORA reanalysis treatment-specific estimate and included it in its base cases. At the second committee meeting, the company noted that in the ZORA reanalysis people could already be on their maximum dose of RAAS inhibitor therapy and would not have the capacity to up-titrate. The EAG accepted there were limitations and uncertainties with the ZORA reanalysis but noted several assumptions made in the company's model when using the Luo study estimates. The EAG noted that in the Luo study all people were assumed to return to optimised RAAS inhibitor therapy, but it was not known how many people up-titrated to an optimal RAAS inhibitor dose (same as with the ZORA reanalysis). The EAG also explained that the Luo study estimate relates to a narrower population of people who restarted RAAS inhibitor treatment after stopping. It also noted the Luo study only included people with chronic kidney disease and did not include people with heart failure. The committee acknowledged there was uncertainty in both the company's and the EAG's sources. It noted that the Luo study related to a very specific population of people who restart treatment. As a result, it was unclear whether the Luo study provided more robust estimates than the ZORA reanalysis. The committee concluded the EAG's approach was more appropriate than the company's approach because it used the same source as the analysis of down-titration rates.

Time constraint for return to maximum RAAS inhibitor state

3.18 The company's model assumed people were only eligible to return to the maximum RAAS inhibitor state if 12 weeks had passed since RAAS inhibitor treatment was stopped or down-titrated (based on clinical expert input from TA599). The EAG's clinical experts had advised that clinicians would consider re-initiating or up-titrating RAAS inhibitor treatment 4 weeks after stopping or down-titration. So, the EAG's base cases used an assumption of 4 weeks. At the second committee meeting, the clinical expert agreed with the EAG's assumption of 4 weeks. The company stated it had used a longer time period to align with the committee's preferred assumptions in TA599 but accepted the EAG's approach. The committee noted that using either the company's or EAG's assumptions had a minimal impact on the ICER. It concluded it would accept the EAG's base-case assumption of 4 weeks to be eligible to return to the maximum RAAS inhibitor state after stopping or down-titration.

Cost-effectiveness estimates

Company and EAG cost-effectiveness estimates

3.19 The company provided the results 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 distribution, the cohort was stratified by the conditions. For sodium zirconium cyclosilicate in the mixed population, the deterministic ICER was £12,495 per QALY gained and the probabilistic ICER 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. In 'EAG base case 2' the probabilities were based on standard care values. At the second committee meeting the EAG updated

its 2 exploratory base cases, which included the updated chronic kidney disease health state costs recalculated by the company (see section 3.16). The EAG's ICER from its base case 1 was £29,475 per QALY gained, and from its base case 2 was £45,895 per QALY gained.

Acceptable ICER

3.20 NICE's manual on health technology evaluations notes that, above a most plausible ICER of £25,000 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 3.6 and section 3.10)
- the assumption that sodium zirconium cyclosilicate impacts the probability of stopping or down-titrating RAAS inhibitor treatment independent of serum potassium levels (see section 3.11).

The committee noted there were uncaptured benefits in the modelling (see section 3.23). It noted the potential to reduce health inequalities by improving outcomes for conditions that disproportionately affect certain groups. And it considered that simplifying the care pathway, including reducing the complexity of monitoring persistent hyperkalaemia, may support management in primary care (see section 3.3 and section 3.24). Because of these factors, the committee concluded that an acceptable ICER would be towards to the higher end of the range NICE considers a cost-effective use of NHS resources (£25,000 to £35,000 per QALY gained).

The committee's preferences

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

- the company's approach of modelling the correlation between serum potassium level and adverse outcomes from SPARK (see section 3.10)
- a lifelong treatment duration for sodium zirconium cyclosilicate, subject to an annual stopping rate (see section 3.12)
- 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 3.13)
- the company's post-consultation scenario in which people in the standard care arm go on to have sodium zirconium cyclosilicate if their serum potassium level is 6.0 mmol per litre or more (see section 3.14)
- that all people are on an optimal RAAS inhibitor dosage at model entry (see section 3.15)
- when people restart RAAS inhibitor treatment, they return to the optimal dosage (see section 3.15)
- the company's post-consultation scenario removing RRT costs from the Kent et al. (2015) estimates for chronic kidney disease stage 4 and 5 (see section 3.16)
- the EAG's approach for estimating the probability of up-titration sourced from the ZORA reanalysis treatment-specific estimates (see section 3.17)
- the EAG's assumption of 4 weeks to be eligible to return to the maximum RAAS inhibitor state after stopping or down-titration (see section 3.18)
- the committee's requested scenario in which the model uses differential RAAS inhibitor therapy rates by treatment arm using the rates from the ZORA reanalysis for the first 3 model cycles (12 weeks). Then, uses the EAG's approach of a single rate by treatment arm for the rest of the model duration using standard-of-care estimates from ZORA (see

section 3.11).

Applying the committee's preferred assumptions resulted in an ICER of £33,725 per QALY gained for the mixed population.

Other factors

Equality

3.22 The company stated it was unable to provide economic modelling for people having long-term dialysis. It stated this was because of the lack 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 of 5.5 mmol per 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 NICE's COVID-19 guideline on 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 people with persistent hyperkalaemia who need dialysis are not usually prescribed potassium binders in the NHS. 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 per litre up to 6.0mmol per litre. In the NHS, people in this group are usually seen in a primary care or

outpatient setting and are distinct from those seen in emergency settings. At the first committee meeting, the committee noted 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 partial review of TA599 focuses on treatment for 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. At the second committee meeting, the committee considered whether the serum potassium thresholds were appropriate for people with chronic kidney disease or heart failure from ethnic minority backgrounds. The company noted that it had previously explored this and stated that hyperkalaemia management does not differ between different ethnic backgrounds. The committee concluded there were no further equality issues.

Uncaptured benefits

3.23 At the first committee meeting, 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. At the second committee meeting, a clinical expert noted that they would likely optimise both RAAS inhibitor use and SGLT-2 inhibitor use for people with chronic

kidney disease and heart failure. They noted that a decision to use sodium zirconium cyclosilicate would unlikely alter SGLT-2 inhibitor use. The committee concluded that this was not an uncaptured benefit

- 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 stated that modelling populations with either chronic kidney disease or heart failure may be conservative because of absence of disutilities applied to standard care for a low potassium diet. The company stated that a low potassium diet negatively impacts quality of life and sodium zirconium cyclosilicate would prevent the need for a low potassium diet. The committee concluded that this was an uncaptured benefit.

  At the second committee meeting, a clinical expert stated that maintaining people on adequate RAAS inhibitor dosing can lead to cardiac remodelling. They noted that if cardiac function improves, people may no longer need expensive cardiac devices. This had not been captured in the modelled costs. The committee acknowledged there were several benefits not captured in the current model. The committee concluded that it would take the potential uncaptured benefits of sodium zirconium cyclosilicate into account in its decision making (see section 3.20). It also recalled that introducing sodium zirconium cyclosilicate had the potential to reduce secondary-care costs through improved management of chronic kidney disease and heart failure (see section 3.24). It recognised that, even with a clear primary-care pathway, some secondary-care input would still be needed and that implementation in primary care may take time because of clinician confidence. The committee considered this an area of uncertainty and agreed to take it into account in its decision making.

Potential to move from secondary care to primary care

3.24 At consultation, stakeholders noted that introducing sodium zirconium cyclosilicate could reduce the need for secondary care. At the second committee meeting, a clinical expert explained that potassium binders can rapidly stabilise severe heart failure, releasing capacity from secondary to primary care. They added that they would expect clinicians in primary care to prefer managing someone with stable heart failure on a binder rather than someone with recurrent hyperkalaemia and worsening symptoms. The clinical expert explained that maintaining optimal RAAS inhibitor therapy slows chronic kidney disease progression and that reducing or stopping treatment increases mortality risk. They noted that GPs are generally willing to offer sodium zirconium cyclosilicate when a clear plan is in place, and that once people are normokalaemic and optimised on RAAS inhibitors, no extra monitoring is needed. They explained that unstable potassium levels lead to frequent tests and GP visits. They advised that access to sodium zirconium cyclosilicate in primary care would support RAAS inhibitor optimisation, reduce the need for repeated monitoring, and increase clinician confidence. The committee acknowledged that these effects could not be quantified and decided that potential reductions in secondary care use and costs should be recognised as uncaptured benefits (see section 3.23). It concluded that it would take this into account in its decision making.

Conclusion

3.25 Applying all the committee's preferred assumptions resulted in an ICER within the range considered to be a cost-effective use of NHS resources. The committee concluded that sodium zirconium cyclosilicate can be used to treat persistent hyperkalaemia in people with chronic kidney disease stage 3b to 5 or heart failure if they have confirmed serum potassium level of at least 5.5 mmol per litre and, because of hyperkalaemia, are not taking an optimised dosage of RAAS inhibitor, and are not on dialysis.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 90 days of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 60 days of the first publication of the final draft guidance.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has persistent hyperkalaemia with a serum potassium level between 5.5 mmol per litre and up to 6 mmol per litre and the healthcare professional responsible for their care thinks that sodium zirconium cyclosilicate is the right treatment, it should be available for use, in line with NICE's recommendations.

5 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, Janet Boadu

Technical leads

Yelan Guo, Mary Hughes

Technical advisers

Jeremy Powell

Project manager

Emily Crowe

Associate director

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