NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Sodium zirconium cyclosilicate for treating hyperkalaemia

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 appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

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

The appraisal 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 race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: April 2019

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 appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document 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 guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 20th May 2019

Third appraisal committee meeting: 30th May 2019

Details of membership of the appraisal committee are given in section 6.

1 Recommendations

1.1 Sodium zirconium cyclosilicate is recommended as an option for treating hyperkalaemia in adults only if:

- it needs treating in an emergency care setting
- the drug is stopped after 28 days of maintenance treatment, or earlier if the hyperkalaemia resolves.

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 clinician consider it appropriate to stop.

Why the committee made these recommendations

Sodium zirconium cyclosilicate is a treatment option for people with high blood serum potassium levels (hyperkalaemia). The company proposes that it would benefit people with heart failure or stages 3 to 5 chronic kidney disease who have high levels of serum potassium. The company also proposes that people may have treatment with sodium zirconium cyclosilicate either in an emergency care or outpatient setting.

There are clinical trials showing that sodium zirconium cyclosilicate is effective in lowering serum potassium levels and can resolve hyperkalaemia in the outpatient setting. However, the trials mostly include people with serum potassium levels that would not be treated in the NHS. There is no clinical evidence to show that sodium zirconium cyclosilicate extends life or improves quality of life compared with standard care in people having treatment in the NHS outpatient setting.

Because of the limitations in the clinical evidence, the cost-effectiveness estimates for sodium zirconium cyclosilicate in the outpatient setting are highly uncertain and likely to be above what NICE normally considers a cost-effective use of NHS

resources. Therefore, sodium zirconium cyclosilicate is not recommended in the outpatient setting for people with hyperkalaemia.

Treating acute life-threatening hyperkalaemia in the emergency care setting is established clinical practice. The company has not presented clinical evidence for hyperkalaemia treated in the emergency care setting. However, evidence from people with high potassium levels having treatment in the outpatient setting is sufficient to show that sodium zirconium cyclosilicate could be a useful intervention in the emergency care setting. Other potassium-lowering treatments are rarely used in this setting because they are poorly tolerated.

The cost-effectiveness estimates for sodium zirconium cyclosilicate in the emergency care setting show that it is a good use of NHS resources. Therefore, sodium zirconium cyclosilicate is recommended as an option for people with hyperkalaemia that needs treating in the emergency care setting.

2 Information about sodium zirconium cyclosilicate

Marketing authorisation indication	Sodium zirconium cyclosilicate (Lokelma, AstraZeneca) has a marketing authorisation 'for the treatment of hyperkalaemia in adult patients'.
Dosage in the marketing authorisation	Correction phase: The recommended starting does of sodium zirconium cyclosilicate is 10 g, administered 3 times a day orally as a suspension in water. When normal serum potassium levels are met, the maintenance regimen should be followed. If normal serum potassium levels are not met within 72 hours of treatment, sodium zirconium cyclosilicate should be stopped Maintenance phase: For people with normal serum potassium levels after the correction phase, the minimal effective dose of sodium zirconium cyclosilicate to prevent recurrence of hyperkalaemia should be established. A starting dose of 5 g once daily is recommended, with possible titration up to a maximum 10 g once daily or down to 5 g once every other day as needed to maintain a normal serum potassium level.
Price	The list price of sodium zirconium cyclosilicate is £14.24 per 10 g sachet or £7.12 per 5 g sachet (DHSC eXchange, maximum list prices, accessed April 2019). Costs may vary in different settings because of negotiated procurement discounts.

3 Committee discussion

The appraisal committee (section 6) considered evidence submitted by AstraZeneca and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

Treatment of hyperkalaemia

Patients in the NHS with serum potassium levels above the normal range do not always need treatment to lower potassium

3.1 Hyperkalaemia is a high level of potassium in the blood. The company defined high serum potassium values as above 5.0 mmol/litre, and the European Resuscitation Council classifies hyperkalaemia as mild (serum potassium level of 5.5 mmol/litre to 5.9 mmol/litre), moderate (6.0 mmol/litre to 6.4 mmol/litre) or severe (6.5 mmol/litre and above). The

committee understood that tests of serum potassium values may incorrectly identify hyperkalaemia, and often need to be confirmed before hyperkalaemia is treated. Hyperkalaemia occurs most commonly in people with chronic kidney disease (stages 4 and 5), heart failure, liver disease, metabolic acidosis, and adrenal insufficiency. It can also occur after treatments for high blood pressure, chronic kidney disease, proteinuria (protein in the urine) and heart failure; these treatments include potassium-sparing diuretics or renin-angiotensin-aldosterone system (RAAS) inhibitors. RAAS inhibitors include angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs) and aldosterone receptor antagonists. Serum potassium levels in people with chronic kidney disease and in people having RAAS inhibitors are routinely monitored. The clinical experts present at the second committee meeting explained that people with heart failure may have treatment for hyperkalaemia at serum potassium levels above 5.5 mmol/litre, whereas people with chronic kidney disease may have treatment at serum potassium levels above 6.0 mmol/litre. They explained that the reason treatment for people with heart failure is considered at a lower serum potassium level than for people with chronic kidney disease is because they are at higher risk from arrythmias, which a sudden change in serum potassium can induce. The committee heard that some people, often those with renal disease, can accommodate high but stable potassium levels. It understood that, once the diagnosis of hyperkalaemia is confirmed, the decision to use a treatment that actively lowers serum potassium takes into account whether the rise in serum potassium is acute and changes on electrocardiogram (ECG). The committee concluded that the company's clinical definition of hyperkalaemia as serum potassium levels above 5.0 mmol/litre was not widely accepted. It also concluded that, unless they need emergency treatment, few patients in the NHS with serum potassium levels above 5.0 mmol/litre have treatment to lower potassium.

The treatment of life-threatening acute hyperkalaemia and chronic hyperkalaemia differs

3.2 The need for, and type of, treatment for hyperkalaemia depends on its severity. Life-threatening acute hyperkalaemia needs emergency treatment in hospital. NICE-accredited clinical practice guidelines for the treatment of acute hyperkalaemia from the UK Renal Association state that the risk of cardiac arrhythmias increases with serum potassium levels above 6.5 mmol/litre. Small rises in serum potassium above this can cause changes on ECG. To lower the risk of cardiac arrest, physicians treat with active potassium-lowering treatments, then identify and remove the cause of hyperkalaemia. The guidelines include the following treatments:

- calcium chloride or calcium gluconate intravenously to protect the heart if there is ECG evidence of hyperkalaemia
- insulin and glucose intravenously, which moves potassium from the blood into cells
- nebulised salbutamol as an adjunctive therapy to insulin and glucose for serum potassium levels of 6.5 mmol/litre and above, which moves potassium from the blood into cells
- after severe hyperkalaemia has resolved, potassium-binding agents may be offered for 3 or more days (namely, calcium resonium given orally) to remove potassium from the body
- stopping or reducing RAAS inhibitors (because these can increase potassium levels).

Chronic hyperkalaemia is treated in an outpatient setting. The aim of treatment is to lower potassium levels to prevent acute hyperkalaemia and hospital treatment. Treatment includes:

- advice to people with chronic kidney disease to avoid foods high in potassium, as part of a wider restrictive diet
- stopping or reducing RAAS inhibitors and potassium-sparing diuretics

- avoiding non-steroidal anti-inflammatory drugs and trimethoprim.

The clinical expert present at the first committee meeting explained that people who have normal serum potassium levels after emergency treatment do not have long-term maintenance treatment with a potassium-lowering drug in current clinical practice. However, he also noted that calcium resonium is poorly tolerated by patients. The committee concluded that managing acute life-threatening hyperkalaemia differs from managing persistently raised but non-life-threatening serum potassium levels, which justified the separate analyses for sodium zirconium cyclosilicate in these populations.

People with chronic hyperkalaemia would welcome an alternative to stopping RAAS inhibitors

3.3 The company proposed that people with chronic hyperkalaemia who take sodium zirconium cyclosilicate would be less likely to stop RAAS inhibitors, so would live longer and have a lower risk of their kidney disease or heart failure getting worse. It did not provide any clinical evidence for this (see section 3.14). NICE's clinical guideline on chronic kidney disease in adults: assessment and management states that RAAS inhibitors should not be 'routinely' started in people with serum potassium levels of 5.0 mmol/litre and above, and should be stopped in people with levels of 6.0 mmol/litre and above. NICE's clinical guideline on chronic heart failure in adults: assessment and management states that serum potassium levels should be monitored before and after starting a RAAS inhibitor or changing RAAS inhibitor dose, but does not specify serum potassium levels at which RAAS inhibitors should be avoided or stopped. The committee and the clinical experts present at both committee meetings agreed that RAAS inhibitors would be used in the NHS for some people with serum potassium levels 5.0 mmol/litre and above and would be stopped when serum potassium levels are 6.0 mmol/litre and above. At levels of serum potassium below 6.0 mmol/litre, the RAAS inhibitor dose would be more likely to be reduced, rather than stopped. This is because

the perceived benefits of being on treatment outweigh the risks of having a serum potassium level of between 5.0 mmol/litre and 6.0 mmol/litre. The committee noted that some people stop RAAS inhibitors for reasons other than hyperkalaemia. The committee concluded that patients and clinicians are keen for new treatments that would allow them to continue RAAS inhibitors.

The long-term benefit of continuing RAAS inhibitors on quality of life and survival in people with hyperkalaemia may vary between patient subgroups

3.4 The clinical expert at the first committee meeting explained that the benefit, or potential harm, of being on RAAS inhibitor treatment depended on: the underlying condition; the class of RAAS inhibitor (ACE inhibitors, ARBs, aldosterone receptor antagonists); and outcome (for example, cardiovascular disease, worsening of renal disease, death). The committee was aware that an NIHR-funded trial is evaluating the potential benefit of withdrawing ACE inhibitors and ARBs in people with stage 4 or 5 chronic kidney disease. The British Society for Heart Failure's response to consultation and a clinical expert present at the second meeting both noted that RAAS inhibitors may be of greater benefit in people with heart failure with reduced ejection fraction compared with people with preserved ejection fraction. The committee acknowledged that, rather than stopping RAAS inhibitor treatment, the dose may be reduced for some people with hyperkalaemia (see section 3.3). It also acknowledged that, for people on more than 1 RAAS inhibitor, it may not be necessary to stop more than 1 to resolve hyperkalaemia. The committee concluded that the harms and benefits of stopping RAAS inhibitors because of hyperkalaemia compared with standard care could be affected by the:

- underlying condition
- type of RAAS inhibitor
- dose of RAAS inhibitor
- number of RAAS inhibitors

- reason for stopping a RAAS inhibitor.

It further concluded that the long-term benefit of continuing RAAS inhibitors on quality of life and survival in people with hyperkalaemia may vary, and that the balance of benefits and harms should be considered in its decision making.

Sodium zirconium cyclosilicate is unlikely to replace a low-potassium diet

3.5 The patient experts noted that maintaining a low-potassium diet is challenging because so many foods contain potassium. The clinical experts explained that they consider the diet worth trying, that it is recommended by NICE, and that it lowers serum potassium compared with an unrestricted diet. They added that a new treatment option would not replace dietary advice but complement it, and may mean that the diet need not be so strict. The committee concluded that sodium zirconium cyclosilicate is unlikely to replace a low-potassium diet.

Company positioning of sodium zirconium cyclosilicate

The company proposes using sodium zirconium cyclosilicate in a population narrower than that in the marketing authorisation

3.6 The marketing authorisation indication for sodium zirconium cyclosilicate specifies ‘treatment for hyperkalaemia’. It was based on the trials presented by the company in which people with serum potassium levels above 5.0 mmol/litre were recruited and had treatment (see section 3.8). The company focused its submission on people with chronic kidney disease (stages 3 to 5, excluding those on dialysis) or heart failure. The committee was aware that some people in the trial may have had both chronic kidney disease and heart failure. It noted that the population in the company’s submission is narrower than the marketing authorisation because the marketing authorisation also includes people with other conditions and milder hyperkalaemia (see section 3.1). The committee concluded that, given the evidence the company chose to present, it

would appraise sodium zirconium cyclosilicate within the population the company proposed, which was narrower than the marketing authorisation.

The company proposes that sodium zirconium cyclosilicate will be used in emergency care for acute, or outpatient care for chronic, hyperkalaemia

3.7 The marketing authorisation for sodium zirconium cyclosilicate covers using it as a corrective treatment for lowering serum potassium levels followed by using it as a maintenance treatment (at a lower dose) for people whose serum potassium levels normalise after the corrective treatment. The maintenance dose aims to avoid repeat hyperkalaemia. The committee noted that the marketing authorisation does not specify whether sodium zirconium cyclosilicate should be used to treat life-threatening hyperkalaemia needing emergency treatment, or persistent hyperkalaemia treated in the outpatient setting. It also noted that it does not specify the level of serum potassium at which treatment should be started. The company proposed that sodium zirconium cyclosilicate would be used:

- In an emergency care setting, as an alternative to calcium resonium and permanently stopping RAAS inhibitors, in people with high levels of serum potassium who need immediate hospital treatment; it explained that sodium zirconium cyclosilicate would complement rather than replace the use of insulin and glucose in patients with life-threatening hyperkalaemia.
- In an outpatient setting, as an alternative to stopping RAAS inhibitors and a strict low-potassium diet to manage chronic hyperkalaemia and prevent it developing into life-threatening hyperkalaemia, in people with hyperkalaemia identified through routine monitoring; the clinical and patient experts did not expect sodium zirconium cyclosilicate to replace the need for a low-potassium diet (see section 3.5).

The company proposed that sodium zirconium cyclosilicate would be started, and RAAS inhibitors stopped or reduced, in people with

persistently high serum potassium levels of 5.5 mmol/litre and above (heart failure) or 6.0 mmol/litre and above (chronic kidney disease). The committee accepted that the levels proposed by the company were intended to align with clinical expert opinion (see section 3.1), but noted that some clinicians may wish to treat hyperkalaemia at alternative serum potassium thresholds. It further concluded that the comparators were both calcium resonium and managing RAAS inhibitors in the emergency care setting, and managing RAAS inhibitors in the outpatient setting.

Clinical effectiveness

Trial evidence does not show whether sodium zirconium cyclosilicate is more clinically effective than NHS standard care

3.8 The clinical-effectiveness evidence for sodium zirconium cyclosilicate came from the ZS004 and ZS005 trials. The trials were done in the outpatient setting, and included some people who would not have treatment in the NHS (because they had lower serum potassium levels than would be treated in the NHS). In its consultation response, the company presented results for 8 patients in ZS004 with serum potassium levels of 6.5 mmol/litre and above, arguing that these patients are likely to have emergency treatment in the NHS. However, the committee noted that, like all the other patients in that trial, they had had treatment as outpatients. Both trials had 2 phases. The first 'correction' phase was single arm (everyone had treatment to lower their serum potassium levels; there was no control group) in patients with serum potassium levels of 5.1 mmol/litre and above. In response to the appraisal consultation document, the company presented data from a third trial, ZS003, which included a placebo-control arm in the 2-day correction phase. The second phase of all 3 trials measured how well sodium zirconium cyclosilicate maintained serum potassium levels in people whose serum potassium levels had responded in the 'correction' phase and were between 3.5 mmol/litre and 5.0 mmol/litre. In ZS004, 'responders' were randomised

to placebo or to continue sodium zirconium cyclosilicate or placebo for 28 days. In ZS005, all 'responders' had sodium zirconium cyclosilicate for 52 weeks. The committee appreciated that the primary outcome measure in all the trials was serum potassium levels. The single-arm maintenance part of ZS005 measured changing use of RAAS inhibitors as an exploratory endpoint. However, the single-arm design of this trial meant that there were no data on whether, compared with standard care, sodium zirconium cyclosilicate allowed a higher proportion of patients to maintain RAAS inhibitors, a key potential benefit suggested by the company (see section 3.3). The committee concluded that the company had not provided any data comparing sodium zirconium cyclosilicate with treatments currently used in the NHS to correct hyperkalaemia and maintain normal serum potassium levels in the outpatient setting (that is, a low-potassium diet and management of RAAS inhibitors). Also, the trials did not reflect treatment of acute hyperkalaemia in hospital. Without these data, it could not determine whether sodium zirconium cyclosilicate is more clinically effective than current standard care in the NHS in either an emergency care or outpatient setting.

Sodium zirconium cyclosilicate could be beneficial in treating acute life-threatening hyperkalaemia

3.9 The committee noted that treating acute life-threatening hyperkalaemia in hospital is established clinical practice. It agreed that lowering potassium levels for patients needing emergency care was a life-saving intervention. The committee therefore concluded that randomised evidence was not needed to show that treating hyperkalaemia in the emergency care setting prolonged life. As such, the uncontrolled evidence showing that sodium zirconium cyclosilicate reduces serum potassium (see section 3.8) is sufficient to conclude that it could be a useful intervention in people with hyperkalaemia needing treatment in the emergency care setting.

It is not clear whether lowering serum potassium is beneficial in chronic hyperkalaemia

3.10 In the correction phase of ZS003, sodium zirconium cyclosilicate was associated with a greater reduction in serum potassium than placebo. The committee was aware that around three-quarters of people in this trial had serum potassium levels below 5.5 mmol/litre, outside the range that would be treated in the NHS. In the correction phases of ZS004 and ZS005, sodium zirconium cyclosilicate was associated with reduced serum potassium levels from above 5.0 mmol/litre to within the normal range of 3.5 mmol/litre to 5.0 mmol/litre in around 70% of patients. In the subgroup of people with serum potassium levels of 6.5 mmol/litre and above, all patients had serum potassium in the normal range after 48 hours of treatment. The average serum potassium in patients in ZS004, over the 28 days after the correction phase, was 5.1 mmol/litre in the placebo group, and 4.8 mmol/litre and 4.5 mmol/litre in the 5 g and 10 g daily doses of sodium zirconium cyclosilicate groups respectively. These all fell within a range that would not be treated further in the NHS. In response to consultation, the company provided a post-hoc analysis of the subgroups of patients in ZS004 and ZS005 who had baseline serum potassium levels of 6.0 mmol/litre and above and 5.5 mmol/litre and above, the threshold at which RAAS inhibitors are likely to be stopped in chronic kidney disease and heart failure respectively. Most patients had a serum potassium under the threshold after the correction phase and maintained this level during the correction phase. The committee noted:

- The placebo response in ZS003 was about one-third of the response with sodium zirconium cyclosilicate.
- The placebo in ZS003 did not reflect NHS practice (for example, using calcium resonium or stopping RAAS inhibitors).
- The trials started treatment in patients with serum potassium levels of above 5.0 mmol/litre. Clinicians in the NHS would not typically offer treatment at this level (see section 3.1).

- Clinicians in the NHS may not always view a serum potassium level of below 5.0 mmol/litre as the target for treatment if serum potassium levels are reduced to non-life-threatening levels, depending on the serum potassium level that precipitated treatment (see section 3.1).
- Symptoms of hyperkalaemia may be similar to symptoms of the underlying condition, for example, heart failure. So, treating hyperkalaemia may not in itself result in a noticeable effect on symptoms.
- The 28 day follow-up period in ZS004 was placebo controlled. The average serum potassium level in patients who were randomised to placebo during this time was around 5.1 mmol/litre, which was lower than the level that would need treatment. It is unclear whether, without further treatment, serum potassium levels would have risen to a level needing treatment after 28 days.
- The follow up in ZS005 was 52 weeks and there is no evidence for the effectiveness of sodium zirconium cyclosilicate beyond this time. The clinical experts stated that, in practice, treatment with sodium zirconium cyclosilicate would be continued indefinitely if the benefits outweighed the potential harms.
- The company did not present any statistical tests for interaction by subgroup, so it was unknown whether patients with chronic kidney disease or heart failure derived greater benefit from sodium zirconium cyclosilicate.

However, the committee concluded that, although the trial results showed that continuing sodium zirconium cyclosilicate was associated with lower serum potassium than stopping sodium zirconium cyclosilicate, the benefit of this to patients with chronic hyperkalaemia was unclear.

Sodium zirconium cyclosilicate is associated with adverse effects

3.11 The company presented data showing that treatment with sodium zirconium cyclosilicate was associated with hypokalaemia, that is low serum potassium. The committee understood that hypokalaemia, like hyperkalaemia, is associated with life-threatening arrhythmias. The committee also noted the wording from the European Medicines Agency that the risk of intestinal perforation is currently unknown but has been reported with polymers that act in the gastrointestinal tract. The committee concluded that sodium zirconium cyclosilicate is associated with adverse effects.

There is insufficient evidence to prove a causal link between lowering serum potassium levels and improving long-term outcomes

3.12 Data were not collected in trials ZS003, ZS004 and ZS005 on the effect of sodium zirconium cyclosilicate on long-term outcomes such as progression of chronic kidney disease or mortality. However, the company proposed in its model that people with hyperkalaemia who have sodium zirconium cyclosilicate live longer than people who do not. This was based on a systematic review of evidence for both chronic kidney disease and heart failure. The company presented evidence from observational cohort studies which showed a higher risk of death, hospitalisation and major adverse cardiovascular events associated with high, but also with lower than normal, serum potassium levels. Using these data, the company assumed that, because patients with higher serum potassium compared with normal values have a higher risk of death, sodium zirconium cyclosilicate prolongs life because it lowers serum potassium. The committee noted that the observational data did not guarantee an independent association between high serum potassium levels and death. It also noted that the observational data did not provide evidence that lowering serum potassium extends life. The committee was aware that these studies could adjust only for known, measured confounders. It also noted that the studies may have been affected by time-dependent

confounding, for example, because increasing serum potassium levels affects RAAS inhibitor use, which in turn affects subsequent serum potassium levels and long-term outcomes. Therefore, RAAS inhibitor use is a time-dependent confounder. The committee was aware that using standard regression adjustment is not appropriate when attempting to estimate causal effects from observational data affected by time-dependent confounding, and noted that the company was unable to show that alternative appropriate methods had been used. It also noted that the authors of a company-supported observational study used in the model cautioned against assuming a causal effect, and acknowledged the possibility of residual confounding. It agreed that a relationship between lowering serum potassium to a normal range and fewer adverse outcomes was biologically plausible for a subset of endpoints. While the company claimed that a randomised trial showed that lowering potassium prolonged survival in people with heart failure, the committee recognised this was a post-hoc observational analysis of a trial cohort. The company did not otherwise provide randomised evidence that lowering serum potassium prolongs life in the outpatient setting. The committee concluded that there was insufficient evidence to prove definitively that lowering serum potassium levels in the outpatient setting leads to improved outcomes.

Stopping RAAS inhibitors likely increases the risk of death, hospitalisation and disease progression

3.13 In addition to proposing clinical benefit because of lowering serum potassium levels (see section 3.12), the company also proposed that people having treatment with sodium zirconium cyclosilicate would live longer and have a better quality of life than people not on treatment. This was because treatment with sodium zirconium cyclosilicate would allow them to maintain or restart treatment with RAAS inhibitors. Based on targeted reviews for chronic kidney disease and heart failure, the company presented data from a network meta-analysis of randomised controlled trials and several observational studies. It assumed that, because these studies showed that starting a RAAS inhibitor is associated

with living longer, people who stop a RAAS inhibitor would have shortened lives. It also presented evidence that RAAS inhibitors are associated with delayed disease progression, and therefore improved quality of life. The committee noted that it would have preferred to have seen a systematic review of the literature. It also noted that it was unclear whether the company had considered in its analyses the factors that may affect the balance of harms and benefits of continuing RAAS inhibitors in people with hyperkalaemia. The committee noted evidence from the clinical experts and from responses to consultation that the benefits of RAAS inhibitors were well established for certain people. It concluded that, in the population being considered, stopping RAAS inhibitors would generally be associated with an increased risk of adverse outcomes and disease progression. The committee concluded that starting RAAS inhibitors prolongs life for many people, so stopping RAAS inhibitors for people who benefit from them would likely shorten life.

There is no evidence that sodium zirconium cyclosilicate prolongs survival in people having treatment for chronic hyperkalaemia

3.14 The committee recalled that serum potassium levels outside the normal range (but below the threshold needing treatment as an emergency in hospital) may increase the risk of mortality (see section 3.12). However, the committee noted that there was no comparative evidence from a randomised trial showing that lowering serum potassium in such people prolonged survival. Stopping RAAS inhibitors may also increase the risk of mortality (see section 3.13). The committee noted that there was also no comparative evidence from clinical trials that RAAS inhibitor use differed between people having sodium zirconium cyclosilicate and people having standard care in the NHS. Therefore, the committee concluded that there was no direct evidence that sodium zirconium cyclosilicate improves survival in people having treatment for chronic hyperkalaemia.

Cost-effectiveness modelling

The company's patient-level simulation model is appropriate

3.15 The company modelled the cost effectiveness of sodium zirconium cyclosilicate using a patient-level simulation model. The model generated a serum potassium trajectory for each patient over time. The proportion of patients who entered the model on RAAS inhibitors was based on the ZS005 clinical trial. Thereafter, RAAS inhibitor use was determined by the patient's serum potassium trajectory. The company chose to model sodium zirconium cyclosilicate as prolonging life in 2 ways: by level of serum potassium (in which treatment led to the full benefit seen in epidemiological studies) and by whether the patient was on a RAAS inhibitor (see sections 3.12 and 3.13). Therefore, patients in the model with normal levels of serum potassium and on RAAS inhibitors on average lived longer and had a better quality of life than patients with higher levels of serum potassium not on RAAS inhibitors. The committee noted that the company modelled 2 settings:

- **Emergency care setting:** patients had sodium zirconium cyclosilicate after insulin−glucose for up to 28 days. The time horizon was 52 weeks.
- **Outpatient setting:** patients had sodium zirconium cyclosilicate for 28 days if it was the first episode of hyperkalaemia or 52 weeks otherwise. The committee understood the company chose 52 weeks because it had no data beyond 52 weeks. The time horizon is lifetime.

  The clinical experts noted that they may only offer people sodium zirconium cyclosilicate for a few days in the emergency care setting, rather than 28 days. In the outpatient setting, they would find it difficult to stop treatment at 52 weeks for fear that serum potassium will increase again.

The committee noted that the company's updated model incorporated some of its preferred assumptions, including:

- serum potassium treatment thresholds that more closely reflect clinical practice in the NHS for chronic kidney disease and heart failure (see section 3.1)
- comparative data for standard of care during the correction phase (from ZS003, see section 3.8)
- modelling a reduction in serum potassium level when patients stop or down-titrate RAAS inhibitors
- costs of changing RAAS inhibitor dose incurred in the outpatient setting
- all patients with a serum potassium level above 6.0 mmol/litre stop RAAS inhibitors for 12 weeks.

The committee concluded that a patient-simulation model was appropriate for decision making.

It is not appropriate to assume that lowering serum potassium in people with chronic hyperkalaemia prolongs life, based only on observational studies

3.16 The company modelled an association between serum potassium levels and the risks of mortality, hospitalisation and major adverse cardiovascular events using observational studies. The committee recalled that the observational studies supporting this assumption did not establish a direct causal link between lowering serum potassium and improved outcomes (or low serum potassium levels and worse outcomes). Also, it was aware that the underlying causes of hyperkalaemia may have led to poor outcomes rather than the hyperkalaemia itself, and that it was unclear whether results from the observational studies had been appropriately adjusted to account for time-dependent confounders (see section 3.12). The committee noted that the company chose a single, company sponsored, study (Luo et al., 2016) rather than a meta-analysis, and that this was a US study rather than a UK study. The ERG assumed no direct effect of potassium levels on outcomes in an exploratory

analysis. The committee agreed that this could be conservative for some endpoints but agreed that this was reasonable without better evidence. It noted that the company had done scenario analysis individually, reducing the increased risk of mortality, hospitalisation or adverse events assumed to be caused by abnormal potassium levels to 80% of the modelled benefit in the company's base case. However, the committee would have preferred to have seen a wider range of scenarios, including its preferred scenario of no benefit, to understand the uncertainty around these parameters. It concluded that it is not appropriate to assume that lowering serum potassium prolongs life in people with chronic hyperkalaemia, based only on observational studies. It would have preferred to have seen how sensitive the estimates of cost effectiveness were to this assumption. Given the uncertainty, the committee concluded that it would like to have seen that sodium zirconium cyclosilicate was cost effective in the absence of an association between serum potassium and adverse outcomes, including death.

The company's approach to modelling the association between RAAS inhibitor use and outcomes is appropriate

3.17 The company modelled an association between use of RAAS inhibitors and the risks of mortality, hospitalisation and major adverse cardiovascular events based on odds ratios from a network meta-analysis of clinical trials of starting RAAS inhibitors (Xie et al., 2016). The committee recalled and accepted evidence from the clinical and patient experts that maintaining RAAS inhibitor therapy is likely to be beneficial for certain patients (see section 3.13). It noted that the company did scenario analyses using alternative data sources and assuming that RAAS inhibitor use had no effect on outcomes. The committee concluded that the company's approach to modelling the association between RAAS inhibitor use and outcomes was appropriate.

The number of people who stop, down-titrate or restart RAAS inhibitors is a source of uncertainty in the model

3.18 The proportion of patients in the model who stopped or down-titrated RAAS inhibitors at specific serum potassium levels, or who restarted RAAS inhibitor therapy, were mostly based on clinical expert opinion and differed between sodium zirconium cyclosilicate and standard care. The committee questioned why the company had not provided more robust data for UK practice, and was concerned about the potential conflicts of interests of the experts consulted by the company. It also recalled that it had not seen evidence that the use of RAAS inhibitors would differ depending on whether patients had sodium zirconium cyclosilicate or standard of care (see section 3.13). It therefore preferred the ERG's assumption that rates of stopping, down-titrating or restarting RAAS inhibitors were the same for all patients. It would also have preferred to have seen evidence for the proportion of patients who stop or down-titrate RAAS inhibitors based on UK studies instead of expert opinion.

The costs of sodium zirconium cyclosilicate would be higher in the NHS in the outpatient setting than is assumed by the company

3.19 The committee recalled that the company assumed that in the outpatient setting, patients would have treatment for up to 1 year, and then sodium zirconium cyclosilicate would be stopped (see section 3.15). It noted that this did not align with the expected use in clinical practice, where treatment would continue indefinitely if there was clinical benefit. It would have preferred to have seen a scenario analysis in which the costs and benefits of sodium zirconium cyclosilicate were modelled beyond 52 weeks. The committee concluded that the company's model underestimated the treatment costs in the outpatient setting. The analyses considered by the committee used the list price for sodium zirconium cyclosilicate. However, the committee noted that, because the drug would only be prescribed in secondary care, then it would be eligible for a patient access scheme discount.

The ERG's exploratory base case is more closely aligned to committee's preferred assumptions

3.20 The committee noted that the ERG's exploratory base case was more closely aligned to its preferred assumptions, including:

- assuming the rate of decline in serum potassium from ZS003 used for standard of care in the model continues over 3 days, matching the number of days of decline in the sodium zirconium cyclosilicate arm
- setting RAAS inhibitor stopping and down-titration rates for standard of care equal to sodium zirconium cyclosilicate because there is no evidence that these would be different between treatments (see section 3.17)
- using the utility values derived by the ERG for chronic kidney disease.

However, as part of the ERG's exploratory base case, the reduced risk of adverse events and death associated with RAAS inhibitors was compared to an active control rather than placebo. The committee agreed that this was not plausible because some people, notably those with hypertension, are unlikely to switch to another active treatment after stopping RAAS inhibitors. It also did not accept the modelled life extension using observational data associating serum potassium levels and mortality. However, overall, the committee concluded that the ERG's base case was more closely aligned to its preferred assumptions.

Cost-effectiveness estimates

Sodium zirconium cyclosilicate is recommended as an option for people who need emergency treatment of hyperkalaemia in hospital

3.21 The committee considered the cost-effectiveness results in the emergency care setting. It recalled that randomised evidence was not needed to show that treating hyperkalaemia in the emergency care setting prolonged life, and that such treatment was standard clinical practice (see

section 3.9). It also agreed that sodium zirconium cyclosilicate reduced serum potassium levels quickly so was a suitable treatment option in this setting. It noted that the drug was associated with lower costs and improved quality of life in both the company's and ERG's base cases and all scenario analyses. It recalled that these results were subject to some uncertainty because there was limited clinical evidence of sodium zirconium cyclosilicate's use in the emergency care setting (see section 3.8) and the gain in quality-adjusted life years (QALYs) was very small. It also recalled that the model used a short time horizon in the emergency care setting so any long-term benefits of sodium zirconium cyclosilicate (such as enabling patients to restart RAAS inhibitors) may have been underestimated. The committee agreed that people with hyperkalaemia would value the option of an alternative treatment to lower serum potassium levels that was better tolerated than calcium resonium (see section 3.2). It therefore concluded that it could recommend sodium zirconium cyclosilicate as an option for people who need treatment for hyperkalaemia in an emergency care setting.

Sodium zirconium cyclosilicate is not recommended as a treatment option in the outpatient setting

3.22 The committee then considered the cost-effectiveness results in the outpatient setting. In recalled that the ERG's alternative base case was more closely aligned to its preferred assumptions (see section 3.20), but that including life extension based on epidemiological studies was not in line with the committee's preferences. The committee noted that the ERG's base case for chronic kidney disease used an odds ratio for RAAS inhibitor outcomes compared with active control (see section 3.20), and that removing this assumption in line with committee's preferences would likely reduce the incremental cost-effectiveness ratio (ICER) by around £1,500 per QALY gained. It noted that the results were highly uncertain because:

- The association between lowering serum potassium levels and improved long-term outcomes was based on observational evidence without sufficient consideration for residual confounding (including time-dependent confounding), and without robust evidence that lowering serum potassium leads to better outcomes (see section 3.12). An exploratory analysis conducted by the ERG removing this association resulted in ICERs of £38,287 per QALY gained in chronic kidney disease and £111,035 per QALY gained in heart failure.
- The company's estimate of the proportions of people that would reduce the dose of or stop RAAS was based on advice from paid clinical experts to the company. The committee would have liked to see a more robust source of data used for these estimates (see section 3.13).

The committee recalled its conclusion that a link between lowering serum potassium levels and improved long-term outcomes was plausible for some outcomes, but unproven (see section 3.16). It agreed that an ICER for decision making would lie near the ERG's scenario analysis removing the association between serum potassium levels and outcomes. The committee would have preferred to have seen evidence that sodium zirconium cyclosilicate was cost effective when this assumption was used. The committee could not determine a most plausible ICER for the outpatient setting because it had not seen scenario analyses that reflected its preferred assumptions. It would also have liked to have seen cost-effectiveness scatter plots to help determine the effect of the uncertainty in the modelled parameters on the cost-effectiveness estimates. The committee also recalled its conclusion that treatment with RAAS inhibitors would improve outcomes but noted that uncertainties around the assumptions of how many patients would down-titrate or restart RAAS inhibitors had not been fully addressed in the company's model (see section 3.17). The committee concluded that, because the modelling assumptions were unsupported by robust evidence, it could not recommend sodium

zirconium cyclosilicate for people with chronic hyperkalaemia in the outpatient setting.

Innovation

The company has not shown that sodium zirconium cyclosilicate is innovative

3.23 The company proposed several benefits of sodium zirconium cyclosilicate, including preventing the need to modify RAAS inhibitor treatment and avoiding a restrictive low-potassium diet. The committee recalled that people would still need to avoid dietary potassium. The patient experts stated that, if the company had shown evidence for these benefits, then sodium zirconium cyclosilicate would be innovative. The committee was aware that other gastrointestinal potassium binders exist and, although these are not well tolerated, sodium zirconium cyclosilicate does not represent a step-change in treatment. The committee concluded, sodium zirconium cyclosilicate could not be considered innovative.

4 Implementation

4.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months 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 recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

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 hyperkalaemia and the doctor 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 Proposed date for review of guidance

5.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Amanda Adler
Chair, Appraisal Committee
April 2019

6 Appraisal committee members and NICE project team

Appraisal committee members

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

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

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

NICE project team

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

Mary Hughes, Alan Lamb
Technical Leads

Ross Dent
Technical Adviser

Jeremy Powell
Project Manager

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