NICE National Institute for Health and Care Excellence

TA599 Sodium zirconium cyclosilicate for treating hyperkalaemia: committee discussion

Evidence review

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Contents

1 Committee discussion

The appraisal committee 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.

Treating hyperkalaemia

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

1.1 Hyperkalaemia is a high level of potassium in the blood. 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 company's clinical trials recruited people with serum (blood) potassium levels above 5.0 mmol/litre. The committee understood that serum potassium tests may incorrectly identify hyperkalaemia, and potassium levels often need to be confirmed. It concluded that any use of sodium zirconium cyclosilicate would be limited to confirmed hyperkalaemia. Hyperkalaemia occurs most commonly in people with chronic kidney disease (stages 4 and 5), and in heart failure. It can also occur after starting treatments for high blood pressure, chronic kidney disease, proteinuria and heart failure, which 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. Clinicians routinely monitor serum potassium in people with chronic kidney disease and in people having RAAS inhibitors. The clinical experts at the second committee meeting explained they would consider drug treatment for hyperkalaemia, if a well-tolerated treatment were available, mainly to optimise the use of RAAS inhibitors. They would consider drug treatment for:

- people with chronic kidney disease and serum potassium levels above 6.0 mmol/litre and
- some people with heart failure and serum potassium levels above 5.5 mmol/

litre.

The committee understood that many people have both heart failure and chronic kidney disease, so it may be appropriate to start drug treatment at the same serum potassium level for both diseases. The committee was not presented with evidence for a differential effect of sodium zirconium cyclosilicate between people with chronic kidney disease and heart failure (see section 1.10). Once the diagnosis of hyperkalaemia is confirmed, the decision to use a treatment that actively lowers serum potassium takes into account whether the hyperkalaemia is life threatening. This is based on whether the rise in serum potassium is acute and whether there are characteristic electrocardiogram (ECG) changes. The committee concluded that most of the people in the company's clinical trials, which recruited people with serum potassium levels above 5.0 mmol/litre, would not have treatment for hyperkalaemia in the NHS.

Treating life-threatening acute hyperkalaemia and chronic hyperkalaemia is different

1.2 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 treating 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 ECG changes. To lower the risk of cardiac arrest, clinicians use 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 to move 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 to move 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, which can increase serum potassium levels.

The aim of treatment of chronic hyperkalaemia is to lower potassium levels to prevent acute life-threatening hyperkalaemia. Treatment includes:

- Advising people with chronic kidney disease to avoid foods high in potassium.
- Stopping or reducing RAAS inhibitors and potassium-sparing diuretics.
- Avoiding non-steroidal anti-inflammatory drugs and trimethoprim.

The clinical expert 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. He also noted that calcium resonium is poorly tolerated by patients. The committee concluded that managing acute life-threatening hyperkalaemia differs from managing persistent but non-life-threatening hyperkalaemia, which justified the separate analyses for sodium zirconium cyclosilicate in these populations.

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

1.3 The company proposed that people with chronic hyperkalaemia who have sodium zirconium cyclosilicate would be less likely to stop RAAS inhibitors. Therefore, they would live longer and have a lower risk of worsening kidney disease or heart failure and death. However, it did not provide any clinical evidence for this (see section 1.10). NICE's guideline on chronic kidney disease: 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 guideline on chronic heart failure in adults: diagnosis 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 the serum potassium levels at which RAAS inhibitors should be avoided or stopped. The committee and the clinical experts at the committee meetings agreed that RAAS inhibitors would be used in the NHS for many 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, clinicians would likely recommend reducing, rather than stopping, the RAAS inhibitor. This is because the perceived benefits of being on treatment outweigh the risks of having a serum potassium level between 5.0 mmol/litre and 6.0 mmol/litre. The committee noted that some people stop RAAS inhibitors for reasons other than hyperkalaemia. It 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

1.4 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 kidney disease, death).

The British Society for Heart Failure's response to consultation and a clinical expert present at the second meeting noted that RAAS inhibitors benefit people with heart failure with reduced ejection fraction, but not people with preserved ejection fraction. 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.

The committee also concluded that the long-term benefit of continuing RAAS inhibitors on quality of life and survival in people with hyperkalaemia may vary and that it would consider the balance of benefits and harms in its decision making.

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

1.5 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; NICE recommends it for people with chronic kidney disease, and 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 sodium zirconium cyclosilicate for a population narrower than that covered by the marketing authorisation

1.6 The marketing authorisation indication for sodium zirconium cyclosilicate specifies 'treatment for hyperkalaemia'. It was based on the company's trials in which people with serum potassium levels above 5.0 mmol/litre were recruited and had treatment (see section 1.8). The company focused its submission on people with chronic kidney disease (stages 3b to 5, excluding those on dialysis) or heart failure (who may also have chronic kidney disease, including stage 3a). The committee noted that the population in the company's submission was narrower than that covered by the marketing authorisation because the marketing authorisation includes people with other conditions. At the third committee meeting, the company proposed that people with confirmed serum potassium levels of 6.0 mmol/litre and above would have treatment. The committee recalled that:

- starting treatment at the same serum potassium level for chronic kidney disease and heart failure may be appropriate (see section 1.1)
- it had not seen evidence justifying different starting levels between chronic kidney disease and heart failure
- 6.0 mmol/litre was the same serum potassium level as that for stopping RAAS inhibitors (see section 1.3).

Therefore, the committee concluded that it would appraise sodium zirconium cyclosilicate for the population and the starting serum potassium level, 6.0 mmol/litre, the company proposed, which was narrower than that covered by the marketing authorisation.

The company proposes that sodium zirconium cyclosilicate will be used alongside standard care for acute hyperkalaemia and

started in specialist care for chronic hyperkalaemia

1.7 The marketing authorisation for sodium zirconium cyclosilicate covers using it as a corrective treatment for lowering serum potassium levels followed by maintenance treatment (at a lower dose) for people whose serum potassium levels return to normal after 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 in outpatient care. The company proposed that sodium zirconium cyclosilicate would be used:

- In emergency care, 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.
- As an alternative to stopping RAAS inhibitors to manage chronic hyperkalaemia and to prevent life-threatening hyperkalaemia, in people with hyperkalaemia identified through routine monitoring. It explained that sodium zirconium cyclosilicate would complement rather than replace a low-potassium diet and may allow such a diet to be less strict (see section 1.5). It also explained that sodium zirconium cyclosilicate would be started in specialist care rather than in general practice.

  The committee concluded that it would appraise sodium zirconium cyclosilicate in the settings the company proposed, and that the comparators were both calcium resonium and managing RAAS inhibitors after emergency treatment, and managing RAAS inhibitors for chronic hyperkalaemia.

Clinical effectiveness

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

1.8 The clinical effectiveness evidence for sodium zirconium cyclosilicate came from the ZS004 and ZS005 trials. The trials were done in outpatient care. They included people who 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 would have emergency treatment in the NHS. However, the committee noted that these patients also had treatment as outpatients, so did not reflect patients who would have treatment in emergency care in the NHS. Both trials had 2 phases. The first 'correction' phase was single arm (everyone had treatment to lower serum potassium; there was no control group) in patients with serum potassium levels of 5.1 mmol/litre and above. The committee recognised that some of the response may have been related to regression to the mean. In response to the first consultation, 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, people whose serum potassium levels had responded were randomised to placebo or to continue sodium zirconium cyclosilicate for 28 days. In ZS005, all people whose serum potassium levels had responded had sodium zirconium cyclosilicate for 52 weeks. The committee appreciated that the primary outcome measure in all the trials was mean serum potassium level. The trials all showed that sodium zirconium cyclosilicate treatment reduced serum potassium level from baseline. The single-arm maintenance part of ZS005 measured changing use of RAAS inhibitors as an exploratory end point. However, the single-arm design of this trial meant that there were no data on whether sodium zirconium cyclosilicate, compared with standard care, allowed more patients to continue on RAAS inhibitors, a key potential benefit suggested by the company (see section 1.3). The committee concluded that the company had not provided any data comparing sodium zirconium cyclosilicate with current NHS treatments to correct hyperkalaemia and

maintain normal serum potassium levels in outpatient care (that is, management of RAAS inhibitors). Without these data, it could not determine whether sodium zirconium cyclosilicate is more clinically effective than current standard care in the NHS for treating chronic hyperkalaemia.

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

1.9 The committee noted that acute hyperkalaemia can be fatal and 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 life-threatening hyperkalaemia in emergency care prolonged life. As such, the uncontrolled evidence showing that sodium zirconium cyclosilicate reduces serum potassium (see section 1.8) was sufficient for the committee to conclude that it could be useful for people with hyperkalaemia needing treatment in emergency care.

There is no direct evidence that sodium zirconium cyclosilicate increases length or quality of life for people having treatment for chronic hyperkalaemia

1.10 The company did 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. This is the threshold at which RAAS inhibitors are likely to be stopped and at which the company proposed sodium zirconium cyclosilicate would be used (see section 1.6). Most patients having sodium zirconium cyclosilicate had a serum potassium value of between 4.0 mmol/litre and 6.0 mmol/litre after the correction phase. For most of these patients, their serum potassium remained within these levels during the maintenance phase. The company also provided data from ZS003, which showed that patients having sodium zirconium cyclosilicate had stable serum potassium levels during the 12-day maintenance period compared with small increases for patients on placebo. The committee noted:

- The placebo in ZS003 did not reflect NHS practice (for example stopping

RAAS inhibitors).

- In ZS003 patients with serum potassium levels of above 5.0 mmol/litre started treatment. Clinicians in the NHS would not typically offer treatment at this level (see section 1.1).
- Symptoms of hyperkalaemia may be similar to symptoms of the underlying condition, for example, heart failure. So, treating hyperkalaemia may not result in a noticeable effect on symptoms.
- ZS005 was the longest trial, with follow up of 52 weeks. The company provided no evidence for the effectiveness of sodium zirconium cyclosilicate beyond 52 weeks. In its updated base case, the company assumed that patients would have the drug indefinitely (see section 1.14), an assumption 1 clinical expert supported.
- 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.

  The committee was also aware that the company claimed that treatment with sodium zirconium cyclosilicate would prolong life and improve quality of life, but none of the trials showed this. The ERG and the consultation responses noted that the company could resolve this uncertainty with a clinical trial designed to report on outcomes such as mortality, disease progression and patterns of RAAS inhibitor use. The company indicated that it was not planning such a trial. The committee concluded that, although the trial results showed that continuing sodium zirconium cyclosilicate was associated with lower serum potassium than stopping the drug, there was no direct evidence that sodium zirconium cyclosilicate improves survival or quality of life over other treatments for people with chronic hyperkalaemia.

Sodium zirconium cyclosilicate is associated with adverse effects

1.11 The company presented data showing that treatment with sodium zirconium cyclosilicate was associated with hypokalaemia, that is low serum potassium. Hypokalaemia, like hyperkalaemia, is associated with life-threatening

arrhythmias. The company explained that treating hyperkalaemia at 6.0 mmol/litre and above was less likely to cause hypokalaemia than when treating it at lower levels. The committee concluded that sodium zirconium cyclosilicate is associated with adverse effects.

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

1.12 Data were not collected in 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 and have a better quality of life than people who do not. This was because treatment with sodium zirconium cyclosilicate would allow them to maintain or restart treatment with RAAS inhibitors. The committee noted that the company provided only exploratory data from a single-arm trial (ZS005) of sodium zirconium cyclosilicate. This showed that most people on RAAS inhibitors continued to have the same dose and some people not on them at the start of the trial had started them by the end of the trial follow up. The committee recalled that there was no evidence showing that RAAS inhibitor dosing was different for people having sodium zirconium cyclosilicate than for people who didn't (see section 1.8). Independent of this, 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. The company 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. The company also presented evidence that RAAS inhibitors are associated with delayed disease progression, and therefore improved quality of life. The committee recognised that the company's evidence addressed the decision problem indirectly. It noted that the trials in the company's literature search compared starting RAAS inhibitors with not starting them, rather than the question relevant to this appraisal, that is, reducing or stopping RAAS inhibitors compared with continuing them. In addition, sodium zirconium cyclosilicate may allow more people to remain on RAAS inhibitors. However, the reason for some people having high potassium levels may be a worsening of the underlying disease, and it is unclear whether the clinical benefit

seen in the trials would translate fully. For example, the committee understood from the clinical expert and consultation responses that the benefits of RAAS inhibitors were well established for certain people, but their benefits were uncertain for others, for example, people close to needing kidney dialysis. 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 was not satisfied that the company had presented robust data on how sodium zirconium cyclosilicate alters dosing of RAAS inhibitors compared with standard care, or the extent to which such alterations improved length and quality of life. However, the committee was also aware of NICE guidance recommending stopping RAAS inhibitors at serum potassium levels of 6.0 mmol/litre and above (see section 1.3). It concluded that starting RAAS inhibitors prolongs life for many people, so stopping them for people who benefit from them would likely shorten life.

There is insufficient evidence to prove that lowering serum potassium levels improves long-term outcomes

1.13 The company also proposed in its model that lowering serum potassium with sodium zirconium cyclosilicate causes people to live longer. It based this on a review of evidence on the association between serum potassium and adverse outcomes for people with chronic kidney disease or heart failure. This evidence, from observational cohort studies, showed that a higher risk of death, hospitalisation and major adverse cardiovascular events was associated with high, but also with lower than normal, serum potassium levels. Using these data, the company assumed that, because people with higher than normal serum potassium 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 causal effect between high serum potassium levels and death. Importantly, even if it did, the committee 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 authors of a company-supported observational study used in the model cautioned against assuming a causal effect, and acknowledged the possibility of residual confounding. At the third committee meeting, the company agreed that these

observational data did not prove causality. The committee agreed that a relationship between lowering serum potassium to a normal range and fewer adverse outcomes was biologically plausible in certain clinical situations. The company did not provide interventional randomised evidence that lowering serum potassium prolongs life in chronic hyperkalaemia. The committee was aware that any association between serum potassium levels and mortality may have been influenced by time-dependent confounding. Specifically, patients with hyperkalaemia may have stopped having RAAS inhibitors, increasing the risk of death. The committee concluded that there was insufficient evidence to prove that lowering serum potassium levels for people in outpatient care improves outcomes.

Cost-effectiveness modelling

A patient-level simulation model is appropriate

1.14 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 ZS005 (36% of people with chronic kidney disease and 70% of people with heart failure). Thereafter, RAAS inhibitor use was determined by the patient's serum potassium trajectory (as below). 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 theoretical benefit seen in epidemiological studies) and by whether the patient was on a RAAS inhibitor (see section 1.12 and section 1.13). The company modelled 2 settings:

- **Emergency care:** patients had sodium zirconium cyclosilicate after insulin–glucose for up to 28 days. The company chose 28 days based on the length of ZS004. The time horizon was 52 weeks.
- **Outpatient care:** patients had sodium zirconium cyclosilicate for 28 days if it was the first episode of hyperkalaemia or for a lifetime, if otherwise. The committee understood the company chose a lifetime duration of treatment because clinical experts stated that treatment would continue as long as

there was evidence of clinical benefit (see section 1.10).

The clinical experts noted that they may offer people sodium zirconium cyclosilicate only for a few days in emergency care, rather than 28 days.

The committee noted that the company's updated base case incorporated some, but not all, of its preferred assumptions, including:

- starting treatment with sodium zirconium cyclosilicate at serum potassium values of 6.0 mmol/litre and above for both chronic kidney disease and heart failure
- comparative data for standard care during the correction phase (from ZS003, see section 1.8)
- modelling a reduction in serum potassium level when patients stop or reduce their dose of RAAS inhibitors
- 80% of patients with a serum potassium level between 5.5 mmol/litre and 6.0 mmol/litre reduce their dose of RAAS inhibitors and 20% stop them
- all patients with a serum potassium level above 6.0 mmol/litre stop RAAS inhibitors for 12 weeks, after which around 50% of people restart them.

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

The company's approach to modelling the association between RAAS inhibitor use and outcomes is appropriate, but the data are inadequate

1.15 The company modelled an association between use of RAAS inhibitors and the risks of mortality, hospitalisation and major adverse cardiovascular events. This was 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 1.12). 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 did not see robust evidence of the effect of sodium zirconium cyclosilicate on RAAS inhibitor use. However, it was aware that clinicians are encouraged to stop RAAS inhibitor treatment in people with serum potassium levels of 6.0 mmol/litre and above. The committee concluded that the company's approach to modelling the association between RAAS inhibitor use and outcomes was appropriate.

It is appropriate to consider the company's scenario removing the association between serum potassium levels and outcomes

1.16 In its base case, 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 that lowering serum potassium improved outcomes. Also, it was aware that the underlying causes of hyperkalaemia may have led to poor outcomes rather than the hyperkalaemia itself. Importantly, it had not been presented with evidence that lowering serum potassium in chronic hyperkalaemia prolongs life. The committee concluded that it was not appropriate to assume that lowering serum potassium prolongs life in people with chronic hyperkalaemia, based only on observational studies relating a surrogate end point to adverse outcomes. The committee also noted that any association between serum potassium level and mortality may have been partially captured in the model. This is because patients in the model with a lower serum potassium level are more likely to be having RAAS inhibitors, and therefore have a decreased risk of death (see section 1.15). The company provided additional scenario analyses reducing the strength of the association from the observational evidence or removing it entirely. The committee concluded that it was appropriate to use the scenario analysis removing the association between serum potassium and adverse outcomes in its decision making.

Cost-effectiveness estimates

Sodium zirconium cyclosilicate alongside standard care is

recommended as an option for people who need emergency treatment of hyperkalaemia

1.17 The committee considered the cost-effectiveness results in emergency care. It recalled that it did not need randomised evidence to show that treating hyperkalaemia in emergency care prolonged life, and that such treatment was standard clinical practice (see section 1.9). The committee was aware that acute hyperkalaemia can be fatal. It agreed that sodium zirconium cyclosilicate reduced serum potassium levels quickly so was a suitable treatment option in emergency care after standard treatments including insulin and glucose (see section 1.2). It recalled that the company had positioned sodium zirconium cyclosilicate to be used alongside standard care for the treatment of life-threatening acute hyperkalaemia (see section 1.7). The committee 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 there was some uncertainty about the results because there was limited clinical evidence of sodium zirconium cyclosilicate's use in emergency care (see section 1.8). Also, the gain in quality-adjusted life years (QALYs) was very small. It also recalled that the model used a short time horizon for this analysis 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 life-threatening hyperkalaemia would value the option of another treatment to lower serum potassium levels that was better tolerated than calcium resonium (see section 1.2). It therefore concluded that it could recommend sodium zirconium cyclosilicate alongside standard care as an option for people needing treatment for acute hyperkalaemia in emergency care.

Sodium zirconium cyclosilicate is recommended as a treatment option for chronic hyperkalaemia

1.18 The committee then considered the cost-effectiveness results for chronic hyperkalaemia. The company's revised base-case incremental cost-effectiveness ratios (ICERs) were less than £20,000 per QALY gained compared with standard care for people with hyperkalaemia who have either chronic kidney disease or heart failure. The exact ICERs cannot be reported here because they are considered confidential by the company. The committee noted that the

company's base case included an association between serum potassium levels and mortality, which the committee did not accept (see section 1.16). However, in the scenario removing this association, the ICERs were also below £20,000 per QALY gained. Therefore, the committee concluded that sodium zirconium cyclosilicate was a cost-effective use of NHS resources for treating chronic hyperkalaemia. The committee noted that, in this scenario, most of the benefits arise because more people are able to have RAAS inhibitors with sodium zirconium cyclosilicate. However, it recalled that some people do not benefit from RAAS inhibitors (see section 1.4), and so concluded that it would not be appropriate for these people to start sodium zirconium cyclosilicate. It further concluded that some people may have to stop RAAS inhibitors for reasons other than hyperkalaemia. The committee concluded that, in these situations, people should also stop having sodium zirconium cyclosilicate. It emphasised that uncertainties remained around the clinical benefit of sodium zirconium cyclosilicate and that these could be addressed by clinical trials.

Innovation

The company did not show that sodium zirconium cyclosilicate is innovative

1.19 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, but did not show evidence of these benefits. 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 that sodium zirconium cyclosilicate could not be considered innovative.

2 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 and Alan Lamb
Technical leads

Ross Dent
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Jeremy Powell
Project manager

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