NICE National Institute for Health and Care Excellence

NICE guidance

Patiromer for treating hyperkalaemia

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Patiromer is recommended as an option for treating hyperkalaemia in adults only if used:

- in emergency care for acute life-threatening hyperkalaemia alongside standard care or
- for people with persistent hyperkalaemia and stages 3b to 5 chronic kidney disease or heart failure, if they:
  - have a confirmed serum potassium level of at least 6.0 mmol/litre and
  - are not taking, or are taking a reduced dosage of, a renin-angiotensin-aldosterone system (RAAS) inhibitor because of hyperkalaemia and
  - are not on dialysis.

1.2 Stop patiromer if RAAS inhibitors are no longer suitable.

1.3 This recommendation is not intended to affect treatment with patiromer 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

Patiromer is a treatment for people with high blood potassium levels (hyperkalaemia). It can be used for adults with chronic kidney disease or heart failure, either:

- in emergency care alongside standard care for acute life-threatening hyperkalaemia or
- for persistent hyperkalaemia if they are able to have RAAS inhibitors.

Treating acute life-threatening hyperkalaemia in emergency care is established clinical practice. Other potassium-lowering treatments are rarely used in this setting because they are poorly tolerated. Patiromer could be a useful addition to emergency care.

Clinical trials show that patiromer lowers serum potassium. But there is no clinical evidence that it extends life or improves quality of life. Patiromer may allow people to stay on RAAS inhibitors (drugs used to treat heart failure and kidney disease) for longer or at a higher dose. This may extend life and improve quality of life.

Considering the benefit from more people being able to stay on RAAS inhibitors, the cost-effectiveness estimates for patiromer suggest that it is a reasonable use of NHS resources. Therefore, it is recommended for treating confirmed persistent hyperkalaemia when started in hospital and alongside standard care for treating acute life-threatening hyperkalaemia in emergency care.

2 Information about patiromer

Marketing authorisation indication

2.1 Patiromer (Veltassa, Vifor Pharma) has a marketing authorisation in the UK 'for the treatment of hyperkalaemia in adults'.

Dosage in the marketing authorisation

2.2 Patiromer is administered orally. The recommended starting dose is 8.4 g once a day and the maximum dose is 25.2 g. The dose can be increased or decreased after a minimum interval of 1 week based on serum potassium levels. The dose should be reduced or stopped if serum potassium is below the desired range. Patiromer should be taken with or without food and separated by 3 hours from other oral medication. The onset of action for patiromer is 4 to 7 hours and patiromer should not replace emergency treatment for life-threatening hyperkalaemia.

Price

2.3 The list price of patiromer is £172.50 per 30-sachet pack, available as 8.4 g sachets or 16.8 g sachets (excluding VAT, Department of Health and Social Care communication, November 2019). Costs may vary in different settings because of negotiated procurement discounts.

3 Committee discussion

The appraisal committee considered evidence submitted by Vifor Pharma 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

3.1 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 committee understood that serum potassium tests may incorrectly identify hyperkalaemia, and hyperkalaemia often needs to be confirmed. It concluded that any use of patiromer would be limited to confirmed hyperkalaemia. Hyperkalaemia occurs most commonly in people with chronic kidney disease (stages 3b, 4 and 5) and in heart failure. It can also occur after starting treatments for high blood pressure, chronic kidney disease, proteinuria (protein in the urine), and heart failure. These 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 on RAAS inhibitors. In response to consultation, the company provided results from a published study which suggested that healthcare practitioners of patients with cardiac or kidney disease would 'take action' at potassium levels of 5.7 or 5.8 mmol/litre. Interviews with cardiologists and nephrologists cited a consensus to down-titrate or stop RAAS inhibitors at serum potassium levels of more than 6.0 mmol/litre. The committee acknowledged that this was in line with NICE's clinical guideline on chronic kidney disease in adults: assessment and management (now replaced by NICE's guideline on chronic kidney disease: assessment and management). The clinical

experts at the second committee meeting explained they would consider drug treatment for hyperkalaemia, if there is a well-tolerated treatment available, mainly to optimise the use of RAAS inhibitors. They would consider drug treatment for:

- people with chronic kidney disease 3b, 4 and 5 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 conditions. It was not presented with evidence for a different effect with patiromer between people with chronic kidney disease and people with heart failure. The company's clinical trials recruited people with serum potassium levels of 5.1 mmol/litre or more. The committee concluded that it was appropriate to focus on level of serum potassium rather than underlying condition, and that most of the people in the company's clinical trials would not have treatment for hyperkalaemia in the NHS (see section 3.8).

Patiromer has a potential role in treating life-threatening acute hyperkalaemia and chronic hyperkalaemia

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 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 electrocardiogram (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 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 for 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 hyperkalaemia has been corrected do not have long-term (maintenance) treatment with a potassium-lowering drug in current clinical practice. This may be because potassium-binding treatments such as calcium resonium are poorly tolerated by patients. The committee was aware that the onset of action for patiromer is 4 to 7 hours after administration and that the summary of product characteristics states that it should not replace emergency treatment for life-threatening hyperkalaemia. The committee considered that patiromer could have a role in treating life-threatening hyperkalaemia alongside usual care. The clinical experts explained that it would not replace intravenous insulin and glucose, but it might replace calcium resonium. The committee concluded that managing acute life-threatening hyperkalaemia and chronic hyperkalaemia differed and that patiromer had a potential role in both.

People with chronic hyperkalaemia would welcome an alternative

to stopping RAAS inhibitors

3.3 The company proposed that people with chronic hyperkalaemia who have patiromer would be less likely to stop RAAS inhibitors than people who do not have patiromer. 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 3.10). NICE's clinical guideline on chronic kidney disease in adults: assessment and management (now replaced by 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 clinical 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 treatment options 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

3.4 The clinical experts 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).

  Specifically, the clinical experts noted that the benefit of RAAS inhibitors in protecting the kidney had not been documented in people with stages 4 and 5 chronic kidney disease. The committee acknowledged that, for some people, the RAAS inhibitor dose may be reduced rather than stopped completely (see section 3.3). Also, some people may be on multiple RAAS inhibitors, for example an ACE or ARB plus an aldosterone receptor, only 1 of which is stopped because of hyperkalaemia. The committee concluded that factors affecting the harms and benefits of stopping RAAS inhibitors because of hyperkalaemia compared with using another antihypertensive (for people with high blood pressure) or standard care (for people who would not normally be offered another blood pressure lowering drug) 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.

Patiromer is unlikely to replace a low-potassium diet but should be used in addition to 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; 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 would complement it, and may mean that the diet need not be so strict. The patient expert stressed at the second meeting that people should be encouraged to continue to follow a low-potassium diet. The committee concluded that patiromer is unlikely to replace a strict low-potassium diet, but should be used in addition to a low-potassium diet.

Company positioning of patiromer

The company proposes patiromer for a population narrower than that covered by the marketing authorisation

3.6 The marketing authorisation indication for patiromer specifies 'treatment of hyperkalaemia in adults'. It was based on the company's trials in which people with serum potassium levels of 5.1 mmol/litre or more were recruited and had treatment (see section 3.8). The company updated its base case in response to consultation to include people with chronic kidney disease (stages 3 to 5, excluding those on dialysis) or heart failure (who may also have chronic kidney disease) and with serum potassium of 6.0 mmol/litre or more in line with clinical expert comments (see section 3.1). The committee heard that, of people with stage 3 chronic kidney disease, those with stage 3b were more likely to develop hyperkalaemia, and more people would likely benefit from RAAS inhibitor compared with people with stage 3a disease. The committee noted that the population in the company's submission was narrower than that covered by the marketing authorisation. The committee recalled that:

- starting treatment at the same serum potassium level for chronic kidney disease and heart failure may be appropriate (see section 3.1)
- it had not seen evidence justifying different starting levels for chronic kidney disease and for heart failure (see section 3.1)
- 6.0 mmol/litre was the same serum potassium level as that for stopping RAAS inhibitors (see section 3.3).

Therefore, the committee concluded that it would appraise patiromer for the population and the starting serum potassium level the company proposed, which was narrower than that covered by the marketing authorisation.

The company proposes that patiromer will be used alongside standard care for acute hyperkalaemia and started in hospital for chronic hyperkalaemia

3.7 The marketing authorisation for patiromer covers using it to lower serum potassium levels. It also specifies that stopping patiromer may result in serum potassium levels rising and treatment should not be stopped without consulting a clinician. The company proposed that patiromer would be used:

- for acute hyperkalaemia, instead of calcium resonium and permanently stopping RAAS inhibitors
- instead of stopping RAAS inhibitors to manage chronic hyperkalaemia and to prevent life-threatening hyperkalaemia, in people with hyperkalaemia identified through routine monitoring. It also explained that patiromer would be started in hospitals.

  The committee noted that the marketing authorisation states that patiromer should not replace emergency treatment for life-threatening hyperkalaemia. It considered that patiromer would not replace standard emergency care for acute life-threatening hyperkalaemia, but it could also be used instead of calcium resonium alongside standard care. The committee concluded that it would appraise patiromer alongside standard care for life-threatening hyperkalaemia, and for confirmed chronic hyperkalaemia.

Clinical effectiveness

Trials do not show that patiromer is more clinically effective than NHS standard care or increases length or quality of life in chronic hyperkalaemia

3.8 The key evidence for the clinical effectiveness of patiromer came from OPAL-HK. This was a phase 3, 12-week, single-blind study that included people with stages 3 and 4 chronic kidney disease, with or without heart failure, who were having a RAAS inhibitor, with serum potassium between 5.1 mmol/litre and 6.5 mmol/litre. The study had 2 parts and its primary outcome was change in serum potassium:

- Part A, 4 weeks (n=243): single-arm dose-ranging study. Everyone had patiromer, and the dosage was adjusted up to a maximum of 50.4 g daily to achieve a target serum potassium between 3.8 mmol/litre and 5.1 mmol/litre.
- Part B, 8 weeks (n=107): randomised, placebo-controlled trial of stopping compared with continuing patiromer, including only people having patiromer whose hyperkalaemia in part A responded (people who had a serum potassium level of 5.5 mmol/litre or more at the beginning of part A and a serum potassium level between 3.8 mmol/litre and 5.1 mmol/litre at the end of part A) and who were still having treatment with a RAAS inhibitor.

  During part A of the study, serum potassium decreased for the total population by 1.01 mmol/litre. In part B of the study, for people whose hyperkalaemia responded to patiromer (as defined above), serum potassium levels were 0.72 mmol/litre higher in the placebo arm than the patiromer arm. However, the serum potassium levels in both arms were not within the range that would be treated in the NHS. Also, part B of the trial addressed stopping patiromer in people already on it whose hyperkalaemia had responded rather than starting patiromer in people who might benefit from it. The company submitted additional clinical evidence in response to consultation, from the PEARL-HF and AMBER trials. However, the ERG noted that the studies were not relevant to the scope of the appraisal because the patients did not have hyperkalaemia at baseline. The committee concluded that the trial evidence did not show patiromer was more clinically effective than current NHS standard care or that patiromer increases length or quality of life for people

having treatment for chronic hyperkalaemia.

Patiromer could be beneficial in treating acute life-threatening hyperkalaemia

3.9 The committee noted that acute hyperkalaemia can be fatal and treating acute life-threatening hyperkalaemia in hospital is established clinical practice. The committee agreed that lowering potassium levels for patients needing emergency care was a life-saving intervention. It 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 patiromer reduces serum potassium (see section 3.8) was sufficient for the committee to conclude that it could be useful for people with hyperkalaemia needing treatment in emergency care, alongside standard care.

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

3.10 Data were not collected in OPAL-HK on the effect of patiromer 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 take patiromer live longer and have a better quality of life than people who do not because treatment with patiromer 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 (OPAL-HK) of patiromer. The company also submitted evidence from AMBER. This was a randomised trial comparing patiromer plus spironolactone with placebo plus spironolactone to see whether patiromer use results in more persistent use of spironolactone (a RAAS inhibitor). It showed that 20% more patients taking patiromer stayed on spironolactone than those taking placebo. However, the patients in the trial did not have hyperkalaemia at baseline; potassium levels were between 4.3 mmol/litre and 5.1 mmol/litre. 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. It

assumed that, because these studies showed that starting a RAAS inhibitor is associated with living longer, stopping a RAAS inhibitor would be associated with dying earlier. The company 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. The committee recognised that worsening underlying disease may lead to worse hyperkalaemia, and that it was unclear whether the clinical benefit seen in the trials would translate to continued use of RAAS inhibitors. 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 patiromer 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's guidance which recommends stopping RAAS inhibitors at serum potassium levels of 6.0 mmol/litre and above (see section 3.3). 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

3.11 The company proposed in its model that lowering serum potassium with patiromer 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, patiromer 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 company did not provide evidence that lowering serum potassium extends life. The committee was aware of DIAMOND, an ongoing randomised controlled trial of patiromer compared with placebo for adults with hyperkalaemia and heart failure. Its primary outcome was time to first occurrence of hospitalisation or death. The DIAMOND trial results may, in future, provide evidence for a link between patiromer and length of life. 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

The company's updated model addresses some of the committee's concerns

3.12 In response to consultation the company made significant revisions to its model. It modelled the cost effectiveness of patiromer using a Markov model with 26 health states, which included stages 3 and 4 chronic kidney disease and end-stage kidney disease (stage 5 chronic kidney disease). Within each chronic kidney disease state patients were grouped into one of 3 serum potassium level categories (less than 5.5 mmol/litre, 5.5 to 6.0 mmol/litre and more than 6.0 mmol/litre). The company also made other changes including:

- only including patients with serum potassium levels of 6.0 mmol/litre or more
- not assuming a direct link between lowering serum potassium and mortality, only an indirect link through continued RAAS inhibitor use
- modelling separate chronic kidney disease health states for stages 3 and 4 (previously modelled as the same health state)
- revising the proportion of hyperkalaemia episodes resulting in hospitalisation from 100% to:
  - 4.5% for people with serum potassium more than 5.0 mmol/litre
  - 6.1% for people with serum potassium between 5.5 mmol/litre and 6.0 mmol/litre and

— 9.1% for people with serum potassium of more than 6.0 mmol/litre.

The committee noted that although the company had attempted to address many of its concerns, some issues remained. These included the rate of recurrence of hyperkalaemia (see section 3.14) and the source of data for stopping patiromer (see section 3.15).

The very limited clinical evidence increases uncertainty

3.13 The company updated the population in its economic model to people with serum potassium of 6.0 mmol/litre or more to match the committee's conclusion about when treatment for hyperkalaemia starts in the NHS (see section 3.1). However, the committee noted that few patients in the OPAL-HK trial had serum potassium levels above 6.0 mmol/litre. This meant that the data for patiromer in the economic model was based on only 26 patients. The committee agreed this was appropriate for people with heart failure and stages 3b, 4 and 5 chronic kidney disease. It was aware that the company had included people with stage 3a chronic kidney disease, but considered that the absolute benefit would be greater in people with stage 3b chronic kidney disease. The committee was also aware that all patients in the OPAL-HK trial had chronic kidney disease and some also had heart failure. It considered that given its conclusion that it was appropriate to focus on the level of serum potassium rather than the underlying condition (see section 3.1), it was likely that the results would also hold for people with heart failure alone. This is because the main benefit of potassium-lowering treatments in chronic hyperkalaemia is to allow people to take RAAS inhibitors, which are beneficial in heart failure. However, the committee concluded that the very limited clinical evidence informing the model increased the uncertainty associated with the cost-effectiveness estimates.

The rate of recurrence of hyperkalaemia used by the company is unrealistically low

3.14 To inform the rate of recurrence of hyperkalaemia in the model, the company used data from the clinical practice research datalink. The ERG highlighted that

the rate of recurrence was very low, between 0.04% to 1.03% per month depending on serum potassium levels and chronic kidney disease stage. This was much lower than the rate in the placebo arm of OPAL-HK. The rate was so low, in part because it was estimated from a large sample of patients in the clinical practice research datalink data with serum potassium lower than 5.5 mmol/litre at baseline. So, it did not reflect the population in the model. To model recurrence in the patiromer arm, the company applied the hazard ratio from the OPAL-HK trial to the annual rate derived from these data. The committee was concerned that, given the very low baseline rate of hyperkalaemia recurrence, the probability of hyperkalaemia recurring increased only slightly when people stopped taking patiromer. It concluded that this was unlikely because patiromer is not disease-modifying, so serum potassium would be expected to increase once treatment stops. It also concluded that the rate of recurrence was unrealistically low for this population. However, the committee was unclear what effect using a higher rate of recurrence would have on the cost-effectiveness results because both patients taking and not taking patiromer would experience more episodes of hyperkalaemia.

The company's source of data for stopping patiromer is not appropriate

3.15 In its updated base case, the company used US claims registry data to model the rate at which people stop treatment with patiromer. Previously it used data from AMETHYST-DN, a 1-year trial of patiromer at different doses in people with type 2 diabetes, chronic kidney disease and serum potassium between 4.3 mmol/litre and 6.0 mmol/litre. The company explained that it had used US claims data because this would better reflect stopping in clinical practice than would randomised controlled trial data from AMETHYST-DN. The ERG explained that the US claims data were unlikely to represent use of patiromer in UK clinical practice because the settings are very different. The ERG continued to use the data from AMETHYST-DN in its base case, in which over half of the patients remained on treatment at 3 years. The ERG also did a scenario analysis using OPAL-HK data to model stopping patiromer. This curve was closer to the US claims data curve, with just under a third of patients on treatment at 1 year. However, the committee noted that the short trial period for OPAL-HK (12 weeks) meant that extrapolating these data is uncertain. The committee considered that the average time on

treatment in the NHS would be longer than seen in the US claims data. This was because the condition of the population in this appraisal, with chronic kidney disease and heart failure and serum potassium greater than 6.0 mmol/litre, was likely to worsen over time. They would therefore need to continue treatment with patiromer while taking RAAS inhibitors. It concluded that the rate at which people stop patiromer was more likely to lie somewhere between the rates based on OPAL-HK and AMETHYST-DN.

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

3.16 The company modelled an association between the 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 benefit certain patients (see section 3.10). The committee did not see robust evidence of patiromer's effect on RAAS inhibitor use. However, it was aware that clinicians are encouraged to stop RAAS inhibitor treatment for people with serum potassium levels of 6.0 mmol/litre and above. The committee considered that any guidance for patiromer would be limited to people who could take RAAS inhibitors. It concluded that the company's approach to modelling the association between RAAS inhibitor use and outcomes was appropriate.

Cost-effectiveness estimates

Patiromer is recommended as a treatment option

3.17 The company's base-case incremental cost-effectiveness ratio (ICER) was £6,774 per quality-adjusted life year gained for patiromer compared with standard care. The committee recalled that this analysis was based on US claims data for stopping patiromer and may not reflect UK clinical practice (see section 3.15). Therefore, the committee also considered the ERG's analyses that

varied the source of data for stopping patiromer:

- ERG's base case: stopping patiromer based on data from AMETHYST-DN, everyone stops treatment at 5 years
- ERG's scenario: stopping patiromer based on data from OPAL-HK.

The committee recalled its conclusion that the rate at which people stop patiromer was likely to lie between the 2 ERG scenarios (see section 3.15). In both ERG scenarios, the ICER was higher than in the company's base case. The committee considered that the model was sensitive to treatment duration because the low baseline rate of recurrence of hyperkalaemia means that longer treatment with patiromer incurs costs which outweigh the benefits (see section 3.14). It therefore considered that with a higher baseline rate of hyperkalaemia recurrence, longer treatment duration may not increase the ICERs as much as in the ERG's analysis. The committee therefore concluded that patiromer was likely to represent a cost-effective use of NHS resources for treating chronic hyperkalaemia and, based on the conclusion in section 3.9, alongside standard care for treating acute hyperkalaemia. It emphasised that uncertainties remained around patiromer's clinical benefit and that these could be addressed by clinical trials (see section 5.1).

Innovation

The company has not shown that patiromer is innovative

3.18 The company proposed several benefits of patiromer but did not show evidence of these. They included not needing to modify RAAS inhibitor treatment and avoiding a restrictive low-potassium diet. The committee was aware that other gastrointestinal potassium binders exist and that patiromer does not represent a step-change in treatment. It concluded that patiromer 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 healthcare professional responsible for their care thinks that patiromer is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Recommendations for research

5.1 The committee noted that there was no clinical evidence showing that having patiromer improved length or quality of life or allowed patients to stay on optimal doses of renin-angiotensin-aldosterone system (RAAS) inhibitors. It therefore considered that it would be valuable to have studies comparing patiromer plus standard care with standard care alone in people with confirmed hyperkalaemia of 6.0 mmol/litre and above, and that these should investigate:

- mortality
- disease progression
- patterns of RAAS inhibitor use
- healthcare utilisation and
- health-related quality of life.

The committee recalled that the DIAMOND trial is ongoing and may help to provide evidence on mortality (see section 3.11). However, the trial is not going to complete until 2022. The committee concluded that the guidance should be reviewed when evidence from DIAMOND is available.

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.

Jessica Cronshaw
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