NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Patiromer 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 patiromer 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?

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 patiromer 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: 19 November 2018

Second appraisal committee meeting: 4 December 2018

Details of membership of the appraisal committee are given in section 5.

1 Recommendations

1.1 Patiromer is not recommended, within its marketing authorisation, for treating hyperkalaemia in adults.

1.2 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 option for people with high blood serum potassium levels (hyperkalaemia). The company proposes that it would benefit people with stage 3 and 4 chronic kidney disease who are having a renin-angiotensin-aldosterone system inhibitor and who have high levels of serum potassium.

Clinical trial results show that, compared with placebo, stopping patiromer in people already having it increases serum potassium levels. However, these results may not be relevant to NHS clinical practice because in the trial most people had a lower level of serum potassium than would be treated in the NHS. There is also no evidence to show that patiromer extends life or improves quality of life compared with standard care in people who would have treatment for hyperkalaemia in the NHS.

Because of the lack of relevant clinical-effectiveness evidence, the cost-effectiveness estimates for patiromer are not valid. Therefore, the drug is not recommended for treating hyperkalaemia in adults.

2 Information about patiromer

Marketing authorisation indication	Patiromer (Veltassa, Vifor Pharma) has a marketing authorisation in the UK 'for the treatment of hyperkalaemia in adults'.
Dosage in the marketing authorisation	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 discontinued if serum potassium is below the desired range. Patiromer should be taken with 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	£300 per 30-sachet pack, each sachet contains 8.4 g of patiromer (excluding VAT; British national formulary online, accessed October 2018). The company has a commercial arrangement, which would apply if the technology had been recommended.

3 Committee discussion

The appraisal committee (section 5) 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.

Treatment of hyperkalaemia

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

3.1 Hyperkalaemia is a high level of potassium in the blood serum, above 5.0 mmol/litre, and is classified by the European Resuscitation Council 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). Hyperkalaemia occurs most commonly in people with chronic kidney disease (stages 4 and 5), heart failure, liver disease and adrenal insufficiency. It can also occur as a result of certain treatments for high

blood pressure, chronic kidney disease, proteinuria (protein in the urine) and heart failure; specifically potassium-sparing diuretics or renin-angiotensin-aldosterone system (RAAS) inhibitors. These 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. Normal serum potassium levels are between 3.5 mmol/litre and 5.0 mmol/litre. However, the clinical and patient experts explained that people do not automatically have treatment to lower serum potassium if it is more than 5.0 mmol/litre. The committee and the clinical experts agreed they would not usually consider treating hyperkalaemia at serum potassium levels lower than 6.0 mmol/litre. This is because levels can be high for several reasons and may resolve fairly quickly without treatment or by treating the cause (rather than the hyperkalaemia itself). The committee understood that the decision to use potassium-lowering treatment would take into account the speed of onset of the hyperkalaemia and changes on electrocardiogram, as well as serum potassium levels, because these affect a patient's prognosis. It concluded that patients in the NHS with serum potassium levels above the normal range do not always have treatment to lower potassium.

Hyperkalaemia is treated as an emergency in hospital or, when it is non-life-threatening, in an outpatient setting: the treatments for these differ

3.2 The need for, and type of, treatment for hyperkalaemia depends on its severity:

- Life-threatening hyperkalaemia treated as an emergency in hospital: in this situation, there is often a rapid onset of very high levels of serum potassium and a risk of cardiac arrest. It is treated with active potassium-lowering treatments, and by identifying and removing the cause. Treatments include:

  - calcium gluconate intravenously to protect the heart from complications of hyperkalaemia
  - insulin and glucose intravenously, which moves potassium from the blood into cells
  - follow-up potassium-binding agents for 3 or more days (namely, calcium resonium given orally) to then remove potassium from the body
  - stopping or reducing RAAS inhibitors (because these can increase potassium levels)

The clinical experts explained that people with normal serum potassium levels after hyperkalaemia has initially been corrected do not have 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.

- Persistently raised, but non-life-threatening hyperkalaemia treated in an outpatient setting: potassium levels may be as high as with life-threatening hyperkalaemia, but that it is less of a risk than when potassium levels have risen quickly. Management aims to lower potassium levels to prevent hyperkalaemia needing 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.

The committee concluded that these populations reflected different decision problems, and should be addressed separately. 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 hyperkalaemia. The committee considered that patiromer could have a role in treating life-threatening hyperkalaemia. It would not replace intravenous insulin and glucose but it might replace calcium resonium. It noted that the company

had not provided evidence for using patiromer with other active treatments for acute life-threatening hyperkalaemia, therefore it could not make decisions on using patiromer in this setting. The committee concluded that managing acute life-threatening hyperkalaemia and chronic hyperkalaemia differed and that patiromer had a potential role in both.

People would welcome an alternative to stopping RAAS inhibitors

3.3 The company proposed that people having patiromer will be less likely to stop RAAS inhibitors, so will live longer with fewer cardiovascular and renal complications. 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 or more, and should be stopped in people with levels of 6.0 mmol/litre or more. The committee noted that some people stop RAAS inhibitors for reasons other than hyperkalaemia. The committee and the clinical experts agreed that RAAS inhibitors would be used in the NHS for some people with serum potassium levels over 5.0 mmol/litre and would be stopped when serum potassium levels are 6.0 mmol/litre or more. At lower levels, the RAAS inhibitor dose would more likely 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 patient and clinical experts explained that some people with high blood pressure may switch to another type of blood pressure lowering treatment if they stop RAAS inhibitors. These may not be as effective for some people in delaying kidney disease. The committee concluded that patients and clinicians were keen for new treatments that would allow them to continue to take RAAS inhibitors, but that the harms and benefits of stopping a RAAS inhibitor and switching to an alternative blood pressure lowering treatment would need to be taken into account.

The long-term benefit of continuing RAAS inhibitors on quality of life and survival in people with hyperkalaemia may vary from person to person

3.4 The clinical experts explained that the benefit of being on RAAS inhibitor treatment depended on: the underlying population (for example, people with different stages of chronic kidney disease); the class of RAAS inhibitor (ACE inhibitors, ARBs, aldosterone receptor antagonists); and outcome (for example, cardiovascular disease, worsening of renal disease, death). Specifically, the clinical experts noted that the benefit of RAAS inhibitors in protecting the kidney had not been documented in people with chronic kidney disease stages 4 and 5. The committee also acknowledged that, in some people, the RAAS inhibitor dose may be reduced rather than stopped completely (see section 3.3) and that 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 for hyperkalaemia compared with using another antihypertensive (for people with high blood pressure) or with standard care (for people who would not normally be offered another blood pressure lowering drug) were affected by the:

- underlying condition
- type of RAAS inhibitor
- dose of RAAS inhibitor
- number of RAAS inhibitors
- reason for stopping 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 from person to person, and that the balance of benefits and harms should be taken into account in its decision-making (see section 3.12).

People with hyperkalaemia would welcome a treatment that allows a less strict low-potassium diet

3.5 The patient experts noted that a low-potassium diet is difficult to stick to because many foods contain potassium. The clinical experts explained that such a diet is considered worth trying to help manage serum potassium levels, and is recommended by NICE. The diet lowers serum potassium compared with an unrestricted diet. They added that a new treatment option would not replace dietary advice but would most likely be used alongside it, and may mean that the diet does not need to be so strict. The committee concluded that, although people may prefer a potassium-lowering drug to a strict diet, patiromer was unlikely to replace a low-potassium diet completely.

Company positioning of patiromer

The company proposes using patiromer in a population narrower than that in the marketing authorisation

3.6 In its submission, the company limited the population to people with hyperkalaemia (serum potassium more than 5.5 mmol/litre) and chronic kidney disease stages 3 and 4 who were having RAAS inhibitors. The committee noted that this population was narrower than that covered by patiromer's marketing authorisation. The patient expert noted that this population excluded people with chronic kidney disease stage 5 or on dialysis. However, there is a need for a treatment in these populations because the severity and frequency of symptoms of hyperkalaemia tend to increase as chronic kidney disease progresses and symptoms could be particularly bad between treatment sessions for people on dialysis. The committee recognised that there was a need for a treatment option for hyperkalaemia for people with chronic kidney disease stage 5 or on dialysis. However it noted that the company had not provided evidence for these populations. The company explained that it chose this population because it matched its key trial for patiromer (OPAL-HK; see section 3.7). It suggested that patiromer would be started in secondary care, but the

clinical experts explained that chronic kidney disease stage 3 is generally managed in primary care. The committee concluded that it would appraise patiromer in the population the company had proposed, which was narrower than the marketing authorisation.

Clinical effectiveness

The key trial does not show whether patiromer is more clinically effective than current standard care in the NHS

3.7 The key evidence for the clinical effectiveness of patiromer came from OPAL-HK. This was a phase III, 12-week, single-blind study that included people with chronic kidney disease stages 3 and 4 who were having a RAAS inhibitor, with serum potassium between 5.1 mmol/litre and 6.5 mmol/litre. The study's primary outcome was change in serum potassium and had 2 parts:

- 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 whose hyperkalaemia responded to patiromer in part A (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 who responded to patiromer (as defined above), serum potassium levels were 0.72 mmol/litre higher than for patients randomised to remain on patiromer. However, the serum potassium levels in both arms were within the range that would not be treated in the NHS and therefore the

difference was not clinically meaningful. The committee recognised that OPAL-HK included patients with serum potassium levels that would not 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 committee concluded that the trial did not show whether patiromer was more clinically effective than current NHS standard care.

The benefit to patients of lower serum potassium levels in OPAL-HK is unclear

3.8 The committee noted that:

- There was no control group in part A, so whether patiromer works better than standard care at returning serum potassium levels to normal is unknown (see section 3.7).
- In the trial, treatment started in patients with serum potassium greater than 5.1 mmol/litre. Clinicians in the NHS would not usually offer treatment at this level (see section 3.1).
- A key outcome for clinicians would be the proportion of people whose serum potassium levels drop to below 6.0 mmol/litre, the level above which NICE's guideline on chronic kidney disease recommends stopping RAAS inhibitors, but this was not an outcome in the trial.
- Hyperkalaemia may be asymptomatic within the range of serum potassium levels in people recruited to OPAL-HK. This means the trial would not fully capture the effect of patiromer on symptoms of hyperkalaemia.
- 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 follow-up in OPAL-HK was short, and at the end of part B (8 weeks), the average serum potassium levels of people who were randomised to placebo was 5.2 mmol/litre, lower than the level that would be treated. Also, the difference in serum potassium levels on

patiromer compared with placebo was not clinically meaningful (see section 3.7). It was unclear whether, without further treatment, serum potassium levels would rise to a level needing treatment.

The committee concluded that, although the trial results showed that continuing patiromer was associated with lower serum potassium than stopping patiromer, the benefit of this to patients in clinical practice was unclear.

The population in OPAL-HK is not generalisable to NHS practice

3.9 The company presented data from the Clinical Practice Research Datalink to characterise people who might need treatment for hyperkalaemia in UK primary care:

- with chronic kidney disease stages 3 and 4 and
- with hyperkalaemia (average serum potassium 5.45 mmol/L) or with heart failure or diabetes and
- on at least 1 RAAS inhibitor.

The ERG explained that these data showed that patients in the NHS are more likely to be men, older and have more comorbidities such as heart failure, hypertension and diabetes than people in OPAL-HK. Also, OPAL-HK had no UK sites and most patients in the trial were from Eastern Europe (65%). The committee did not consider that the effect of potassium lowering would vary by geographical site. However, clinical practice may vary and the trial clinicians were unblinded, so stopping RAAS inhibitors could vary by geographical site. The ERG explained that all patients in the OPAL-HK trial were white and there was no evidence of people from other ethnic groups taking part. The committee considered that there was no reason for the efficacy of patiromer to differ by ethnic group. It noted that NICE's guidance on hypertension in adults: diagnosis and management recommends calcium channel blockers as the first treatment option over RAAS inhibitors in people of African or Caribbean family origin with untreated high blood pressure, so there may be fewer

people of African or Caribbean family origin taking RAAS inhibitors in clinical practice than from other ethnic groups. However, clinical experts explained that people with chronic kidney disease represent a population on many antihypertensive agents and that at this point in the treatment pathway they did not expect to see a difference in RAAS inhibitor use between ethnic groups. The committee concluded that patients in OPAL-HK were not representative of patients seen in NHS clinical practice.

The OPAL-HK protocol for managing hyperkalaemia differs by treatment arm and does not reflect clinical practice

3.10 In OPAL-HK part B, more people stopped RAAS inhibitors in the placebo arm (52%) than in the patiromer arm (5%). This supported the company's proposal that patiromer allows people with chronic kidney disease to maintain optimal RAAS inhibitor treatment. However, the committee recalled its earlier conclusion that the population did not reflect the population who would have treatment in the NHS (see section 3.6). Also, the company acknowledged that managing RAAS inhibitors differed in OPAL-HK between the patiromer arm and the placebo arm. In the placebo arm after the first hyperkalaemic event (at a potassium level of more than 5.5 mmol/litre), the dosage of RAAS inhibitor was reduced. Whereas in the patiromer arm after the first hyperkalaemic event, the dosage of patiromer was increased and the dosage of RAAS inhibitor was not changed. The committee was aware that stopping the RAAS inhibitor was an exploratory endpoint in the trial and the trial was not designed to look at the effect of patiromer on maintaining an optimal RAAS inhibitor dosage. Therefore, the committee recognised that any findings were not confirmatory. Also, the rate of stopping RAAS inhibitors was much higher than that provided by the company from UK primary care data (Clinical Practice Research Datalink, see section 3.9). This showed that over 3 years 25% of people stopped their RAAS inhibitor compared with 56% in 8 weeks in the OPAL-HK placebo arm. The ERG noted that this was partly because of more frequent (weekly) monitoring of serum potassium levels in the trial than in clinical practice. The committee noted a further

limitation; clinicians in the trial were unblinded and this would contribute to bias between the study arms in stopping rates for RAAS inhibitors. The committee recognised that the placebo arm may not reflect NHS practice, in which RAAS inhibitors may be stopped in a population with chronic kidney disease at values of serum potassium closer to 6.0 mmol/litre than to 5.5 mmol/litre. The committee concluded that the trial was not designed to assess the use of RAAS inhibitors and the differences seen were mostly driven by a different protocol for stopping RAAS inhibitors between patiromer and placebo.

The company submission is not relevant to NHS clinical practice

3.11 The marketing authorisation for patiromer does not state a serum potassium level at which treatment should start. However, the company submission stated that treatment would start if serum potassium was more than 5.5 mmol/litre (see section 3.6). The committee concluded that the company had focussed its submission on a population with serum potassium levels reflecting a wider range than would usually be treated in the NHS (see section 3.1). Also, OPAL-HK included people with even lower serum potassium levels. The committee agreed that focussing on people with serum potassium levels of 6.0 mmol/litre or more would reflect clinical practice in the NHS.

There is no evidence that patiromer prolongs survival

3.12 OPAL-HK did not collect data on the effect of patiromer on long-term outcomes such as progression of chronic kidney disease, cardiovascular events or mortality. Yet the company proposed that people who take patiromer live longer than people who do not take patiromer, using data from a range of literature sources. These included:

- Published data from a US observational cohort study (Luo et al. 2016) showing a higher risk of death associated with high (5.5 mmol/L or more) and low (less than 3.9 mmol/L) serum potassium levels compared with a reference value of 4.5 mmol/litre to 4.9 mmol/litre.

- Published data from a network meta-analysis of randomised controlled trials comparing survival when people started treatment with a RAAS inhibitor with placebo. The company assumed that because this meta-analysis showed that starting a RAAS inhibitor is associated with living longer, people who stop having a RAAS inhibitor have a shorter life expectancy.

The company suggested that because the OPAL-HK trial showed that people having patiromer maintained serum potassium levels in the normal range (3.8 mmol/litre to 5.1 mmol/litre) and more people stayed on RAAS inhibitor treatment in the patiromer arm, then they are also less likely to develop worse chronic kidney disease, have cardiovascular events or die, based on the associations reported in the US observational data. The committee noted several limitations associated with the company's assumptions:

- There was no evidence for a difference in serum potassium levels on standard care and while having patiromer for a population who would have NHS treatment.
- There was no comparative evidence from a randomised trial that lowering serum potassium in people with hyperkalaemia prolonged survival.
- The company provided evidence from a single observational study showing an association between serum potassium levels and death, but it did not provide a systematic review of the evidence.
- The committee recognised that this observational evidence does not guarantee an independent association between high serum potassium and death or evidence that lowering serum potassium extends life. It noted that people with hyperkalaemia may have differences in other clinical characteristics compared with people without hyperkalaemia, which may also increase their risk of death. These differences may be unmeasured or unknown, and the extent to which the company took these into account was unclear.

- The normal range (as defined by the company; 3.8 mmol/litre to 5.1 mmol/litre) overlapped with the category of serum potassium (3.5 to 3.9 mmol/litre) associated with an increased risk of death compared with serum potassium values of 4.5 mmol/litre to 4.9 mmol/litre. The committee was concerned that if the associations between serum potassium and death were true, using patiromer to lower serum potassium to the levels proposed by the company could actually increase the risk of death.
- It was unclear whether the benefits of starting RAAS inhibitors on survival and progression of chronic kidney disease (assessed in the network meta-analyses) were the same as the risks of stopping RAAS inhibitors to manage serum potassium levels. This is because patients may change to another antihypertensive drug.
- It was unclear whether the company had taken into account in its analyses the factors that may affect the balance of harms and benefits of continuing RAAS inhibitors in people with hyperkalaemia (see section 3.4).

The committee concluded that the evidence did not support patiromer treatment extending life.

Cost-effectiveness modelling

The model does not generate valid estimates of cost effectiveness for the NHS

3.13 In the company's model patients accrued quality-adjusted life years (QALYs) mainly by gaining quality of life from delayed progression to end-stage renal disease and fewer hyperkalaemic events, and by extending survival from delayed progression to end-stage renal disease and death. It was aware that the ERG had amended the model including:

- correcting a discount to the price of patiromer and
- correcting the probability of hyperkalaemic events from daily to monthly.

The model's outputs were not useful for decision-making because the results were driven by the assumed surrogate relationship between serum potassium levels and mortality and other long-term outcomes (see section 3.8). Because this relationship was very uncertain, the cost-effectiveness results lacked validity. Also the population in the model, and therefore the cost-effectiveness results, could not be generalised to NHS clinical practice.

It is not appropriate to use clinical-effectiveness data for people starting RAAS inhibitors to model people stopping treatment with RAAS inhibitors

3.14 The company used data from a network meta-analysis of randomised trials (Xie et al. 2016) to estimate the risk of progressing to end-stage renal disease, death or having a cardiovascular event for people on RAAS inhibitors compared with people stopping treatment with RAAS inhibitors. The network meta-analysis included estimates of the effects of RAAS inhibitors compared with placebo and compared with other active controls. The company used the estimates of RAAS inhibitors compared with placebo in the model. However, the ERG explained that it would be more appropriate to use the estimates comparing RAAS inhibitors with an active control. This was because after stopping RAAS inhibitors people are usually offered an alternative antihypertensive drug in clinical practice (see section 3.3). The committee considered that the ERG's estimates that compared starting RAAS inhibitors with an active control were more appropriate than the company's estimates that compared starting RAAS inhibitors with placebo. However, the estimates still did not represent the effect of continuing with, compared with stopping, a RAAS inhibitor. It concluded that there was considerable uncertainty associated with the benefit of continuing a RAAS inhibitor and this was likely to be overestimated in the model.

The company overestimated the risk of progressing to end-stage renal disease

3.15 The company estimated the risk of progressing to end-stage renal disease for people with stage 3 and 4 chronic kidney disease from data that

included people with end-stage renal disease (chronic kidney disease stage 5). The estimated monthly transition probability was 1.4%. The ERG preferred to use estimates that included patients with stage 3 and 4 chronic kidney disease only, which gave a lower probability estimate of 0.39%. The committee noted that the company's estimate included people who would be considered to have end-stage renal disease already and so it concluded that the company's estimate did not reflect the risk of progressing to end-stage renal disease.

It is inappropriate to assume that fewer people start on RAAS inhibitors in the placebo arm than in the patiromer arm

3.16 The key driver of cost effectiveness in the model was the proportion of people who take (start or continue) RAAS inhibitors in the patiromer arm compared with the placebo arm. The company assumed that the proportion of people on RAAS inhibitors in the economic model was the same as the proportion remaining on RAAS inhibitors at the end of part B in OPAL-HK, that is, 69% in the patiromer arm (pooled value for people whose hyperkalaemia responded and did not respond) and 48% in the placebo arm. The ERG preferred that all patients started the model on RAAS inhibitors in both the placebo and patiromer arms. The committee recognised that the population presented by the company included people taking RAAS inhibitors and therefore agreed that everyone in the model should start on a RAAs inhibitor.

The proportion of episodes of hyperkalaemia that result in hospitalisation is overestimated in the company's and ERG's economic model

3.17 The company assumed in its economic model that 100% of episodes of hyperkalaemia (serum potassium more than 5.5 mmol/litre) resulted in hospitalisation. The ERG adjusted the estimate to 24.3% in line with the paper cited by the company, Thomsen et al. 2017. The clinical experts explained that in clinical practice far less than 24.3% of people with a serum potassium of more than 5.5 mmol/litre would be hospitalised. The committee considered that these estimates would be more appropriate for

a population with life-threatening hyperkalaemia. The committee concluded that both the company and ERG overestimated the proportion of people with hyperkalaemia who would be hospitalised.

Adverse events should be included in the economic model

3.18 The company did not include any adverse events in its model. In OPAL-HK part B, gastrointestinal events and hypomagnesaemia were more common in people remaining on patiromer than in people on placebo. Additionally, the committee considered that a group with chronic kidney disease or heart failure or both was at higher risk for hypomagnesaemia than a general population, because a higher proportion would have treatment with proton-pump inhibitors. The committee agreed that it was not appropriate to exclude adverse events from the economic model.

Cost-effectiveness estimates

It is not possible to determine a plausible cost-effectiveness estimate

3.19 The committee considered the company's and the ERG's cost-effectiveness results. It agreed that the current evidence did not address how and when hyperkalaemia would be treated in the NHS. Moreover, the committee recognised that the company had not shown that patiromer extends life or increases quality of life in people without life-threatening hyperkalaemia (see section 3.12). Therefore, the committee concluded that the estimates of cost effectiveness were not relevant for decision-making. It considered that without better clinical evidence, any revisions to the modelling would not strengthen the evidence going into the model. The committee concluded that it could not recommend patiromer as a cost-effective use of NHS resources.

Innovation

The company has not shown that patiromer is innovative

3.20 The company presented the proposed benefits of patiromer. These included not needing to modify RAAS inhibitor treatment and to follow a

restrictive low-potassium diet. The patient experts stated that had the company shown these benefits for patiromer then the drug would be innovative. The committee concluded that the clinical effectiveness and the benefits of patiromer had not been shown and, because of this, it could not be considered innovative.

4 Proposed date for review of guidance

4.1 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
October 2018

5 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
Technical Lead

Ross Dent
Technical Adviser

Jeremy Powell
Project Manager

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