Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2264

patiromer (as patiromer sorbitex calcium) 8.4g and 16.8g powder for oral suspension (Veltassa®)

Vifor Fresenius Medical Care Renal Pharma UK Ltd

9 October 2020

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a resubmission

patiromer (Veltassa®) is not recommended for use within NHSScotland.

Indication under review: for the treatment of hyperkalaemia in adults.

In a clinical study, patients with chronic kidney disease (CKD) and hyperkalaemia who were taking at least one renin-angiotensin-aldosterone system (RAAS) inhibitor, were treated with patiromer for four weeks. Patients who had responded to patiromer (with normalisation of serum potassium concentrations) were then randomised to either continue patiromer, or placebo. Patiromer treatment during this withdrawal phase was associated with a significant change in serum potassium concentrations after four weeks, when compared with placebo.

The submitting company did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Vice Chairman
Scottish Medicines Consortium

Indication

For the treatment of hyperkalaemia in adults.[1]

Dosing Information

The recommended starting dose is 8.4g, orally, once daily. The daily dose may be adjusted in intervals of one week or longer, based on the serum potassium level and the desired target range. The daily dose may be increased or decreased by 8.4g as necessary to reach the desired target range, up to a maximum dose of 25.2g daily. If serum potassium falls below the desired range, the dose should be reduced or discontinued.

Administration of patiromer should be separated by 3 hours from other oral medicinal products.

The onset of action of patiromer occurs 4 to 7 hours after administration. Patiromer should not replace emergency treatment for life threatening hyperkalaemia.[1]

Product availability date

5 October 2017

Summary of evidence on comparative efficacy

Patiromer is a non-absorbed cation-exchange polymer that contains a calcium-sorbitol complex as a counterion. It binds to potassium in the colonic lumen, reducing intestinal potassium reabsorption, increasing faecal potassium excretion, lowering total body potassium which leads to a reduction in serum potassium levels.[1, 2] The submitting company has requested that SMC considers patiromer when positioned for use in patients with stage 3 or 4 chronic kidney disease (CKD), with or without heart failure, with a serum potassium level of >6.0mmol/L who are receiving or require renin angiotensin aldosterone system (RAAS) inhibitors.

The key clinical evidence for this indication is the OPAL-HK study, a multicentre phase III study comprising two phases: a single-arm, 4-week treatment phase, followed by an 8-week, placebo-controlled, randomised-withdrawal phase. The study was single-blinded; patients were advised that they would receive patiromer at some point during the study but were unaware of treatment allocation during both phases of the study. The study recruited 243 adults (up to 80 years of age) with hyperkalaemia (serum potassium concentration ≥5.1mmol/L and <6.5mmol/L), stage 3 or 4 CKD (estimated Glomerular Filtration Rate [eGFR] ≥15 to <60mL/min/1.73m^2) and on a stable dose of at least one RAAS inhibitor. Doses of other anti-hypertensive medication also had to be stable for at least four weeks prior to screening.[2, 3]

All patients in the treatment phase were allocated to patiromer at one of two doses based on the severity of their baseline hyperkalaemia (measured by local laboratories): 8.4g / day in patients with potassium concentration 5.1 to <5.5mmol/L (mild hyperkalaemia, n=92) and 16.8g / day in

those with potassium concentration ≥5.5 to <6.5mmol/L (moderate to severe hyperkalaemia, n=151). Patiromer was taken in two divided doses; this was titrated according to locally-measured serum potassium concentrations up to a maximum daily dose of 50.4g / day in accordance with the pre-specified study algorithm to maintain serum potassium in the target range (3.8 to <5.1mmol/L). RAAS inhibitor(s) dosage was maintained, but was discontinued if serum potassium concentration was ≥6.5mmol/L. Treatment decisions were made at weekly intervals, unless the potassium concentration was ≥6.5mmol/L (reviewed after 24 hours), or there was a second consecutive potassium concentration <3.8mmol/L or between 5.5mmol/L and <6.5mmol/L which was reviewed after 72 hours.[2, 3]

In the 4-week treatment phase of the study, the primary outcome was the mean change in serum potassium concentration from baseline to week 4, based on central laboratory measurement, assessed in a modified intention-to-treat (mITT) population (n=237), consisting of patients who received at least one dose of patiromer and had at least one post-baseline serum potassium measurement. The mean baseline serum potassium concentration was 5.6mmol/L; mean change from baseline to week 4 was -1.01mmol/L (95% confidence interval [CI]: -1.07 to -0.95), p<0.001 in the mITT population. In patients with mild hyperkalaemia at baseline (n=90), the mean change was -0.65mmol/L (95% CI: -0.74 to -0.55) and in patients with moderate to severe hyperkalaemia (n=147) -1.23 (95% CI:-1.31 to -1.16). The proportion of patients with serum potassium concentrations within the target range of 3.8 to <5.1mmol/L, at week 4 was 76%. The proportion was similar regardless of the baseline severity of hyperkalaemia; 74% in the mild hyperkalaemia (5.1 to 5.8mmol/L) group and 77% in the moderate hyperkalaemia (≥5.8mmol/L) group.[2, 3]

Patients who completed the treatment phase were eligible to enter the randomised-withdrawal phase if their baseline potassium concentration (measured by central laboratory) was ≥5.5mmol/L, their concentration at week four of the treatment phase was between 3.8mmol/L and <5.1mmol/L, they had been on 8.4g to 50.4g / day of patiromer and continued to take a RAAS inhibitor.[2, 3]

Patients who entered the randomised-withdrawal phase were randomised in a 1:1 ratio to patiromer (at the dose taken during week four of the treatment phase, n=55) or placebo (n=52). Randomisation was stratified according to baseline serum potassium concentration (5.5mmol/L to <5.8mmol/L, or ≥5.8mmol/L) and presence of type 2 diabetes mellitus. An algorithm specified how to manage recurrent hyperkalaemia (≥5.5mmol/L in the first four weeks and ≥5.1mmol/L in weeks five to eight, measured in local laboratories) either through dose modification of patiromer, or the RAAS inhibitor (in the placebo group). Subsequent hyperkalaemia events required discontinuation of the RAAS inhibitor and / or discontinuation of study treatment. Hypokalaemia (<3.8mmol/L) at any point required discontinuation of study treatment.

The primary efficacy endpoint in the randomised-withdrawal phase was the between-treatment-group difference in median change in serum potassium concentration from the start of the withdrawal phase to week 4, or to the earliest visit at which the patient's serum potassium (measured locally) was <3.8mmol/L or ≥5.5mmol/L (when an intervention was made).

Results for this outcome, and the two secondary outcomes of this phase, analysed in the ITT population, are presented in Table 1.

Table 1: Primary and secondary outcomes from the randomised-withdrawal phase of the OPAL-HK study (ITT population)[2, 3]

		patiromer (n=55)	placebo (n=52)
Primary Outcome	Mean serum potassium level at start of withdrawal phase (baseline)	4.49mmol/L	4.45mmol/L
	Median change in serum potassium level from baseline to week 4*	0mmol/L	0.72mmol/L
	Between-group difference	0.72mmol/L (95% CI: 0.46 to 0.99) p<0.001	
Secondary outcomes	Proportion of patients with at least one serum potassium concentration ≥5.5mmol/L from baseline up to week 8.≠	15%	60%
	Proportion of patients with at least one serum potassium concentration ≥5.1mmol/L from baseline up to week 8.≠	43%	91%

*or to the earliest visit at which the patient's serum potassium (measured locally) was <3.8mmol/L or ≥5.5mmol/L.
≠p-value versus placebo <0.001. CI = confidence interval

The potential for patiromer treatment to facilitate ongoing RAAS inhibitor treatment was investigated as an exploratory outcome. During the randomised-withdrawal phase of the study, 16% of patients in the patiromer group required an intervention to manage recurrence of hyperkalaemia compared with 62% of placebo patients. Fifty-two percent (52%) of patients receiving placebo discontinued RAAS inhibitor treatment due to recurrent hyperkalaemia, compared with 5% of subjects treated with patiromer. RAAS inhibitors were still used by 94% and 44% of patiromer-treated patients and placebo patients, respectively, at the end of the withdrawal phase. At the start of the withdrawal phase, 38% of patiromer patients and 40% of placebo patients were judged to be on maximal dose RAAS inhibitor.[2, 3]

Subgroup analyses generally found that the treatment effect of change in serum potassium was similar in patients with and without heart failure during the initial treatment and randomised-withdrawal phases of the study. In addition, during the randomised-withdrawal phase, in the subgroup of patients with heart failure, 11% (3/27) of patiromer and 59% (13/22) of placebo patients required an intervention for recurrence of hyperkalaemia and 100% and 55% of patients respectively were still receiving RAAS inhibitor therapy at the end of week 8. These results should be treated with caution since these outcomes were exploratory and this phase of the study was not powered for subgroup analysis.[3, 4]

To support the proposed positioning, the company provided results from post hoc analyses of OPAL-HK, in 14% (35/243) of patients who entered the treatment phase and 24% (26/107) of patients randomised during the treatment-withdrawal phase who had a baseline serum potassium

level of >6.0mmol/L and stage 3 or 4 CKD. SMC is unable to publish the results from the post hoc analyses that were used to inform the economic model.

The AMETHYST-DN phase II study provides supporting evidence of patiromer efficacy over a treatment period of one year. This multi-centre, open-label, dose-ranging study recruited 306 adults (aged 30 to 80 years) with type 2 diabetes mellitus and CKD (eGFR 15 to <60mL/min/1.73m^2), with or without hypertension who were receiving an angiotensin converting enzyme (ACE) inhibitor and / or an angiotensin II receptor blocker (ARB). Eligible patients (with serum potassium concentration >5.0mmol/L to <6.0mmol/L) were stratified by severity of hyperkalaemia and randomised to receive patiromer doses ranging from 8.4g / day up to 33.6g / day. Doses were titrated to maintain serum potassium concentration ≤5.0mmol/L. After 52 weeks, the proportion of patients with normokalaemia (serum potassium concentration within the range 3.8 to 5.0mmol/L) was 86% in those with mild hyperkalaemia at baseline, and 90% for those with moderate hyperkalaemia at baseline. The proportion of patients who required a dose reduction or discontinuation of RAAS inhibitors was not reported.[2, 6]

A randomised, double-blind, phase III study (DIAMOND) is currently underway to determine if treatment with patiromer compared with placebo in patients who developed hyperkalemia while receiving RAAS inhibitors will result in continued use of RAAS inhibitors in line with heart failure treatment guidelines and so decrease the occurrence of the combined endpoint of cardiovascular death and cardiovascular hospitalisation. The primary outcome is time to first occurrence of cardiovascular death or cardiovascular hospitalisation (or equivalent in outpatient clinic). Secondary outcomes include the proportion of patients on ≥50% of guideline-recommended target dose of RAAS inhibitors at the end of the study and the total number of heart failure hospitalisations (or equivalent in outpatient clinic). It is estimated that the study will be completed in March 2022 and the results will help to provide evidence on the mortality associated with the risk of hyperkalaemia in patients with heart failure.[7]

*Other data were also assessed but remain confidential.**

Summary of evidence on comparative safety

No active comparative safety data are available.

During the treatment phase of the OPAL-HK study, adverse events (AEs) were reported in 47% (114/243) of patients; AEs led to discontinuation of patiromer in 6.2% (15/243) of patients.[3] In the randomised-withdrawal phase, similar proportions of patients reported at least one AE, 47% (26/55) and 50% (26/50) of patiromer and placebo patients, respectively. One patient in each group discontinued study treatment due to AEs.

In the treatment phase, the most common AEs were gastrointestinal: constipation (11% of patients), diarrhoea (3.3%) and nausea (3.3%). In the withdrawal phase, these AEs were also reported in 3.6% of patients randomised to patiromer and by no patients in the placebo group.

The incidence of hypokalaemia (serum potassium concentration <3.5mmol/L) was low. In the treatment phase this AE occurred in 3.0% of patients. In the randomised withdrawal phase hypokalaemia (serum potassium concentration <3.8mmol/L) occurred in 5.5% and 1.9% of patiromer and placebo patients, respectively.

ECG changes associated with hyperkalaemia were observed in two patients during the treatment phase of the study. Serious AEs occurred in three patients in the treatment phase (one of which was a conduction disorder, atrial fibrillation); all were considered by investigators to be unrelated to treatment.

Monitoring of other biochemistry revealed no clinically relevant changes in renal function, calcium, fluoride and bicarbonate. Magnesium-replacement therapy was commenced in 3.7% of patients during the treatment-phase of the study.[3]

In the AMETHYST-DN study (n=304), the most common AEs over the one-year follow-up period were: worsening of CKD (9.2%), hypomagnesemia (8.6%), worsening hypertension (7.9%), constipation (6.3%), diarrhoea (5.6%) and hypoglycaemia (3.3%).[6]

Summary of clinical effectiveness issues

Serum potassium levels usually range between 3.5 and 5.0 mmol/L. There is no agreed definition of hyperkalaemia. The UK Renal Association recommends using the European Resuscitation Council Guideline definitions, which define hyperkalaemia as serum potassium > 5.5 mmol/L, with mild elevations defined as 5.5 to 5.9 mmol/L, moderate as 6.0 to 6.4 mmol/L and severe as ≥ 6.5 mmol/L. The level of raised serum potassium at which treatment is initiated can be influenced by clinical considerations, including co-morbidities. [8] Patients with chronic kidney disease (CKD) are particularly susceptible to hyperkalaemia for a number of reasons: reduced elimination due to reduced glomerular filtration of potassium, redistribution of potassium into the extracellular space due to metabolic acidosis, high dietary potassium intake relative to residual renal function, and use of medication that alters potassium homeostasis in the body (for example those affecting the RAAS such as angiotensin-converting enzyme [ACE] inhibitors, or angiotensin-II receptor antagonists [ARBs]). In addition patients with CKD may have important co-morbidities that increase the risk of hyperkalaemia further: diabetes (reduced insulin action reduces ability to distribute potassium into the intracellular space), cardiac failure (reduced cardiac output reducing renal perfusion) and / or cardiovascular disease in which treatments are associated with hyperkalaemia (ACE inhibitors, mineralocorticoid receptor antagonists, cardiac glycosides). It is estimated that 5% to 50% of patients with renal insufficiency have hyperkalaemia and the prevalence increases as renal function declines.[2] There is a significant evidence base in favour of RAAS inhibition for a range of long-term conditions including CKD and chronic heart failure. Clinical guidelines recommend that if other factors have been addressed, ACE inhibitors / ARBs should be discontinued in the presence of ongoing hyperkalaemia (serum potassium ≥5.5mmol/L in chronic heart failure, and ≥6.0mmol/L in CKD).[9, 10]

The management of hyperkalaemia in patients with CKD includes dietary modification, use of sodium bicarbonate to correct metabolic acidosis, diuretics, and medication review to avoid medicines associated with hyperkalaemia. Clinical practice guidelines on the treatment of acute hyperkalaemia in adults suggests that calcium polystyrene sulfonate is not used in the emergency treatment of severe hyperkalaemia, but may be considered in patients with moderate hyperkalaemia. Sodium zirconium cyclosilicate is recommended and patiromer is suggested as an option for the emergency management of acute life-threatening hyperkalaemia. Sodium zirconium cyclosilicate and patiromer are also recommended as an option for the outpatient management of persistent hyperkalaemia (serum potassium ≥6.0mmol/L) in patients with stage 3b to 5 CKD or heart failure receiving a suboptimal dose of RAAS inhibitor. [8] Several other guidelines also address the management of milder hyperkalaemia in non-urgent care settings. These include recommendations to discontinue or reduce the dose of RAAS inhibitor, which may be temporary. Patiromer is one of several cation exchange medicines for the treatment of hyperkalaemia, including calcium polystyrene sulfonate (Calcium Resonium®), sodium polystyrene sulfonate (Resonium A®) and sodium zirconium cyclosilicate (Lokelma®).[11-13] The EMA notes that there are limited prospective, long-term data on the use of calcium and sodium polystyrene sulfonate; that they are poorly tolerated (adverse effects include intestinal necrosis, and sodium excess with sodium polystyrene sulfonate) and are complicated to use in a chronic condition (they require intense monitoring as they are contraindicated in normokalaemia).[2] The submitting company has requested that SMC considers patiromer when positioned for use in patients with stage 3 or 4 chronic kidney disease (CKD), with or without heart failure, with a serum potassium level of >6.0mmol/L who are receiving or require RAAS inhibitors. Clinical experts consulted by SMC advised that patiromer addresses an unmet need in this therapeutic area, namely a satisfactory treatment for hyperkalaemia with concomitant RAAS inhibitor use.

In the key OPAL-HK study, in patients with hyperkalaemia, CKD and continuing RAAS inhibitor treatment, the addition of patiromer reduced serum potassium concentrations by a mean of 1mmol/L after 4 weeks and approximately 75% of patients achieved serum potassium concentrations in the normal range during this treatment phase. In the subgroup of patients with baseline serum potassium concentration ≥5.5mmol/L who had responded to patiromer, the study demonstrated that ongoing treatment maintained the reduction in serum potassium concentration, and was associated with a significantly lower proportion of patients experiencing recurrent hyperkalaemia compared with withdrawal of treatment (the placebo group). Although the median change in serum potassium concentration was 0mmol/L in the patiromer group during the randomised-withdrawal phase of the study, actionable hyperkalaemia (serum potassium concentration >5.5mmol/L) developed in 15% of patiromer patients.[3] Evidence to support the positioning proposed by the company comes from a post hoc subgroup analysis in a small number of patients.

The study had a number of limitations including its small sample size for a commonly encountered clinical scenario. This may be due to the choice of biochemical outcome with the study sufficiently powered to demonstrate differences in serum potassium concentrations. During the withdrawal phase, last observation carried forward was used to impute the week four data for patients who

had a serum potassium outside the range of 3.8mmol/L to 5.5mmol/L prior to week four (and who had a treatment intervention during the first four weeks of the phase). The true magnitude of the treatment effect was not measured. The EMA noted that the size of the treatment benefit should be treated with caution; it stated that the secondary endpoints better reflected the study design. No patient-reported outcomes were assessed. The OPAL-HK study was limited to 12 weeks and since patiromer would most likely be used as part of the patient's chronic disease management, longer-term data are desirable. The phase II AMETHYST-DN study, provides supporting data for using patiromer over one year; however the data are non-comparative and were not from a patient population who had hyperkalaemia. The studies employed a twice-daily dosage regimen. The EMA considered the pharmacodynamic data, patient convenience, and potential for drug-drug interactions; it was satisfied that an once-daily regimen was appropriate for the marketing authorisation for patiromer. Patients in the OPAL-HK study received doses as high as 50.4g daily but the maximum licensed dose is 25.2g daily and the mean dose for patients with moderate hyperkalaemia in OPAL-HK was 21.4g. The use of higher than licensed doses of patiromer in the study may affect the application of the results.[1, 2, 6]

The exclusion of some groups of patients from OPAL-HK, who may be considered to have a need for RAAS inhibition (for example those with recent cardiovascular events, and severe heart failure) reduces the generalisability of the study results to clinical practice. The positioning proposed by the company includes patients with or without heart failure, but OPAL-HK excluded patients with NYHA class IV heart failure.[3] OPAL-HK did not permit concomitant use of sodium bicarbonate; the generalisability of the study results for patients already managed with this modality is unclear. There are no comparative data with other cation exchange resins.

The ability to continue RAAS inhibitor therapy was assessed as an exploratory outcome in the OPAL-HK study. At the start of the treatment phase of the study only 44% of patients were considered to be on "maximal dose" RAAS inhibitor. The contribution of hyperkalaemia to the designation of "maximal dose" was not reported.[2, 3] The study was not designed to demonstrate any direct health outcome from continuing RAAS inhibition, such as improved mortality, cardiovascular event prevention, or morbidity associated with heart failure or CKD progression, nor did the study permit optimisation of RAAS inhibition to target doses that are associated with greatest health gains. The PEARL-HF study provides evidence of patiromer enabling the titration of spironolactone in normokalaemic patients with chronic heart failure who were at risk of hyperkalaemia.[14] There are no data for patiromer facilitating the titration of ACE inhibitors or ARBs. Evidence from the ongoing DIAMOND study is awaited to provide clinically relevant long-term data on the use of patiromer to manage hyperkalaemia in heart failure patients receiving RAAS inhibitors.[7]

The summary of product characteristics (SmPC) notes that since onset of action of patiromer occurs 4 to 7 hours after administration, patiromer should not replace emergency treatment for life threatening hyperkalaemia. The SmPC also notes that there are limited data in patients with an eGFR of <15mL/min/1.73m^2 and in patients who are receiving dialysis and that no special dose and administration guidelines were used for such patients during clinical studies.[1]

Clinical experts consulted by SMC considered that patiromer is a therapeutic advance given the potential to facilitate RAAS inhibitor treatment.

The administration of patiromer is complicated by the potential for drug-drug interaction through the binding of medicines in the gastrointestinal tract. It is recommended that there is a three-hour window between patiromer and other oral medicines. This may be challenging for patients with CKD who are likely to encounter polypharmacy. Incomplete adherence may mean patients would be vulnerable to dangerously high levels of potassium and associated risks. A potential complication of patiromer treatment is low serum magnesium concentrations; patients should be monitored for this for at least one month after starting patiromer and may require oral supplementation.[1]

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis evaluating patiromer versus standard of care (SoC) for the treatment of hyperkalaemia in adult patients with stage 3-4 CKD, with or without heart failure (HF), who have a serum potassium level of >6.0 mmol/L and are receiving or require RAAS inhibitor therapies. Standard of care was defined as dietary modification and RAAS inhibitor dose modification.

A twenty-six state Markov model was developed to model the costs and consequences for eligible patients over a lifetime time horizon (35 years using a one month cycle length). Health states were defined by a combination of CKD stage, cardiovascular (CV) event status and serum potassium levels. Patients enter the model via one of two health states with a serum potassium level of >6.0 mmol/L and are distributed between these according to the prevalence of CKD stages 3 and 4 in the OPAL-HK study. At the end of cycle 1, patients may transition from their initial health state into one of three different serum potassium categories (<5.5 mmol/L, 5.5-6.0 mmol/L or >6.0 mmol/L). However, it is assumed that CKD stage does not change during this cycle. For cycle 2 onwards, there are a number of different possible transitions: a patient may transition between serum potassium categories (in a stepwise manner only), experience progression of their CKD (e.g. CKD stage 3 to 4) or experience a cardiovascular event (stroke or myocardial infarction). The perspective of NHS Scotland and Social Care was adopted.

Clinical effectiveness data were estimated from a combination of the OPAL-HK study and an analysis conducted using the Clinical Practice Research Datalink (CPRD). In particular, a sub-group of patients (n = 26) from the treatment phase of the study was used as the basis for estimating cycle 1 transition probabilities from the two initial health states for patiromer whereas the CPRD was used to estimate parallel probabilities for SoC. For cycle 2 onwards, transition probabilities between low serum potassium levels (<5.5 mmol/L) and mid serum potassium levels (5.5-6.0 mmol/L) were estimated using data from the randomised withdrawal phase of OPAL-HK for both patiromer and SoC. However, transition probabilities between mid serum potassium levels and high serum potassium levels (>6.0 mmol/L) were calculated using data from the CPRD, with equal probabilities assumed for both patiromer and SoC. The probabilities for CKD progression and

experiencing a CV event were derived from a published network meta-analysis.[15] Other adverse clinical outcomes (e.g. hospitalisation) and treatment related adverse events were also included in the model.

A published utility equation was used to estimate a set of gender-weighted baseline utility values by age.[16] These were subsequently adjusted by applying health state utility values for CKD stage, adverse clinical outcomes (e.g. cardiovascular events) and additive disutilities for treatment related adverse events. A separate study collected information regarding patients' health states via the EQ-5D-questionnaire within a prospective observational study of the relationship between health-related quality-of-life, progression to end-stage renal disease and mortality.[17] Data were collected from 745 participants recruited into the UK-based study to the end March 2014. Health states were converted into an EQ-5D index score using a set of weighted preferences specific to the UK population. A multicentre, non-interventional, longitudinal evaluation of health utility in patients experiencing acute coronary syndrome or stroke events was also used. ED-5D surveys were sent to patients (≥18 years) from three centres in the UK, 1 month following hospital admission for myocardial infarction, unstable angina or stroke.[18] No information is provided regarding the valuation of the health state information collected in this study. A variety of sources are applied to incorporate disutility associated with adverse events.

Medicines acquisition costs were applied for patiromer and SoC, where applicable. However, no wastage was applied for patiromer. Patients receiving patiromer were assumed to receive treatment indefinitely subject to discontinuation for reasons which are not stated. Additional resource components included inpatient stays, blood tests, outpatient visits and management of adverse events. These were generally appropriate, although limited details were provided regarding disease state-specific costs.

The base case cost-effectiveness results are presented in Table 2.

Table 2: Revised base-case cost-effectiveness results

Setting	Costs			QALYs			ICER
	Patiromer	Standard care	Δ	Patiromer	Standard care	Δ	
Base case	£44,405	£44,028	£377	5.1835	5.1548	0.0287	**£13,154**
Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; Δ, incremental.							

A number of scenario analyses were included alongside their revised base case results, and additional scenarios previously requested were also provided on this basis. The key scenarios are presented in Table 3. These highlight that the model is highly sensitive to the time horizon selected, probability of hospitalisation due to hyperkalaemia, treatment duration and source of discontinuation data.

Table 3: Scenario analyses using revised base-case

Scenario	Description		ICER
Base case			£13,154
1	Relative risk for serum potassium transition probabilities from cycle 2 onwards equal 1 (i.e. no difference in relative effectiveness)		£16,846
2	Hyperkalaemic events do not result in hospitalisation		£26,525
3	Time horizon	3 months	Dominated
4		1 year	£2,454,942
5		5 years	£38,248
6		20 years	£13,258
7		35 years (base case)	£13,154
8	Source of discontinuation data	AMETHYST-DN	£147,954
9		OPAL-HK	£1,497
10	Treatment duration (no discontinuation)	1 month	Dominant
11		3 months	Dominant
12		1 year	£41,083
13		5 years	£143,321
14		7 years	£166,842
15		35 years	£227,306
Abbreviations: ICER, incremental cost-effectiveness ratio			

There are several weaknesses and uncertainties with the economic analysis:

- The primary outcomes in the OPAL-HK study are largely related to changes in serum potassium levels. This is of limited use in an economic evaluation where benefits are accrued according to changes in long-term health outcomes. Furthermore, this study was short-term, requiring the extrapolation of clinical evidence from a 3-month clinical trial to a 35 year lifetime time horizon. The impact of using a shorter time horizon has a significant upwards impact on the ICER as shown in scenario analyses 3 to 6 in table 3. Following the New Drugs Committee meeting, the company conducted a survey of 11 Scottish clinicians and noted that this found support for a key benefit of reducing serum potassium being the longer term benefits from the safe prescribing of heart failure medication. While noted, this remains a key uncertainty.
- The clinical effectiveness of patiromer and SoC are derived from a combination of different sources, creating uncertainty regarding the estimates of relative effectiveness due to differences in patient populations. Furthermore, the sample sizes used to estimate clinical effectiveness are relatively small. The impact of this on cost-effectiveness results is unclear.
- There is uncertainty regarding the treatment duration and discontinuation profile of patiromer expected in clinical practice. A longer treatment duration, assuming no discontinuation, significantly increases the ICER as shown in scenarios 12 to 15 in table 3. The company noted that the aforementioned survey conducted with Scottish clinicians found support for the treatment durations that were modelled in the base case analysis.

Due to these weaknesses and uncertainties the economic case has not been demonstrated.

*Other data were also assessed but remain confidential.**

Summary of patient and carer involvement

The following information reflects the views of the specified Patient Groups.

- We received patient group submissions from Kidney Research UK and Pumping Marvellous Foundation. Both organisations are registered charities.

- Kidney Research UK has received 16.5% pharmaceutical company funding in the past two years, including from the submitting company. The Pumping Marvellous Foundation has received 71% pharmaceutical company funding in the past two years, including from the submitting company.

- Hyperkalaemia is a serious medical condition that can cause severe cardiac electrophysiology alterations, such as cardiac arrhythmias, and sudden death. Patients living with the condition feel worried that if their condition gets worse they could face a cardiac event or even premature death. The most common symptoms include: extreme tiredness or weakness, a feeling of numbness or tingling, nausea or vomiting, trouble breathing, chest pain and palpitations or irregular heartbeats. Many heart failure patients and their families are unaware of their susceptibility to raised potassium and do not know the symptoms or red flags.

- Patients with hyperkalaemia normally manage their condition with multiple treatments. Kidney patients are already taking many medicines for comorbidities and are often on dialysis due to end stage kidney failure. This adds to the overall burden of side effects and emotional/mental pressure, especially for older and vulnerable patients. For chronic or recurrent hyperkalaemia, most treatment options are limited to low potassium diet, diuretics and modification of hyperkalaemia-inducing medicines, such as RAAS inhibitors. Patients struggle with most dietary measures, therefore adherence is an issue and often impossible for many patients.

- A licensed medicine that would help control long-term raised potassium levels will offer hope to those patients who have struggled to maintain an appropriate diet. Patiromer may also enable patients to continue taking life preserving heart and kidney medicines, which would otherwise have to be modified or discontinued due to their side effects.

Additional information: guidelines and protocols

The UK Renal Association published updated clinical practice guidelines for the treatment of acute hyperkalaemia in adults in June 2020. This guidance uses the same European hyperkalaemia classifications as the position statement published by Think Kidneys, the Renal Association, and the British Society for Heart Failure. The guideline makes the following relevant recommendations. In primary care, patients with severe hyperkalaemia (potassium ≥6.5mmol/L) are admitted to hospital for immediate assessment and treatment. Calcium polystyrene sulfonate is not used in the emergency treatment of severe hyperkalaemia, but may be considered in patients with moderate hyperkalaemia. Sodium zirconium cyclosilicate is recommended, and patiromer is suggested, as an option for the emergency management of acute life-threatening hyperkalaemia. Sodium zirconium cyclosilicate or patiromer is recommended as an option for the outpatient management of persistent hyperkalaemia (serum potassium ≥6.0mmol/L) in patients with stage 3b to 5 CKD or heart failure receiving a suboptimal dose of RAAS inhibitor (or also not receiving RAAS inhibitors due to hyperkalaemia in the case of patiromer). RAAS inhibitors should be stopped in patients with serum potassium ≥6.0 mmol/L who do not meet the criteria for sodium zirconium cyclosilicate or patiromer. In patients with mild hyperkalaemia (potassium ≥5.5-5.9mmol/L), increased monitoring is recommended along with consideration of dose reductions of RAAS inhibitors. It is recommended that RAAS inhibitors are used with caution if serum potassium is >5.0 mmol/L and are withheld during acute illness (for example sepsis, hypovolaemia and/or acute kidney injury) at all severities of hyperkalaemia.[8]

In March 2016 the Scottish Intercollegiate Guidelines Network (SIGN) issued publication number 147, Management of chronic heart failure: A national clinical guideline. This guidance, which pre-dates the availability of patiromer, notes that some rise in urea, creatinine and potassium is to be expected after initiation of an ACE inhibitor; if an increase is small and asymptomatic no action is necessary. An increase in potassium up to 5.5 mmol/L and an increase in creatinine of up to 50% above baseline or 266micromol/L are acceptable. If urea, creatinine or potassium do rise excessively consider stopping concomitant nephrotoxic drugs (for example, NSAIDs), other potassium supplements or retaining agents (triamterene, amiloride, spironolactone, eplerenone) and, if there are no signs of congestion, reducing the dose of diuretic. If greater rises in creatinine or potassium persist despite adjustment of concomitant medications, the dose of the ACE inhibitor should be halved and blood urea, creatinine and electrolytes rechecked within one to two weeks. If potassium rises to >5.5 mmol/L or creatinine increases by >100% or to above 310micromol/l the ACE inhibitor should be stopped and specialist advice sought.[9]

A position statement entitled Changes in kidney function and serum potassium during ACEI (angiotensin converting enzyme inhibitors)/ARB (angiotensin receptor blocker)/diuretic treatment in primary care was published by Think Kidneys, the Renal Association, and the British Society for Heart Failure in October 2017. This statement identified that hyperkalaemia is common in patients with chronic kidney disease especially if patients are treated with ACEI, ARB, mineralocorticoid receptor antagonists (MRA) (e.g. spironolactone), or NSAIDs. It is recommended that management

in primary care depends on the severity of hyperkalaemia and on the clinical context. Hyperkalaemia is classified as follows:

- Severe hyperkalaemia = serum potassium ≥6.5mmol/L
- Moderate hyperkalaemia = serum potassium 6.0 to 6.4mmol/L
- Mild hyperkalaemia = serum potassium 5.5 to 5.9mmol/L

The position statement recommends that patients with severe hyperkalaemia and patients with moderate and mild hyperkalaemia who are acutely unwell are referred to acute care. In clinically stable patients with moderate or mild hyperkalaemia the statement recommends that a review of medications should be undertaken. In those with moderate hyperkalaemia this would include immediately stopping any ACEI, ARB or MRA and repeating serum potassium within 1 week and in those with mild hyperkalaemia consider halving dose or one or both of any ACEI, ARB or MRA, consider halving dose of one or both. This should be followed by a review of indications. (NB patients should not be treated with combinations of ACEI and ARB). If these medicines are used for hypertension, consider an alternative antihypertensive drug. If these medicines are used for heart failure with reduced ejection fraction or kidney disease with albuminuria, re-start at a lower dose once serum potassium < 5.5mmol/L and then continue to monitor: if the patient was on a combination of ACE or ARB and an MRA, only re-start one of these drugs at a time. If the dose has been reduced continue these medicines and monitor.[19]

The European Society of Cardiology published Guidelines for the diagnosis and treatment of acute and chronic heart failure in 2016. These guidelines include a section on hyperkalaemia and recommends that management of acute hyperkalaemia (6.0mmol/L) may require a short-term cessation of potassium-retaining agents and RAAS inhibitor, but this should be minimised and RAAS inhibitor should be carefully reintroduced as soon as possible while monitoring potassium levels. The guideline noted that two new potassium binders, patiromer and sodium zirconium cyclosilicate, were under consideration for regulatory approval and initial results from patients with heart failure were available, which confirm the efficacy of these therapies in reducing serum potassium and preventing recurrent hyperkalaemia in patients with heart failure and CKD in the context of treatment with RAAS inhibitor.[20]

In January 2015 the National Institute for Health and Care Excellence (NICE) published an updated version of Clinical Guideline 182: Chronic kidney disease in adults: assessment and management. This guidance which pre-dated the availability of patiromer makes the following relevant recommendations:

- Do not routinely offer a RAAS inhibitor to people with CKD if their pretreatment serum potassium concentration is greater than 5.0mmol/L.
- When hyperkalaemia precludes use of renin–angiotensin system antagonists, assessment, investigation and treatment of other factors known to promote hyperkalaemia should be undertaken and the serum potassium concentration rechecked.
- Concurrent prescription of drugs known to promote hyperkalaemia is not a contraindication to the use of renin–angiotensin system antagonists, but be aware that

more frequent monitoring of serum potassium concentration may be required.

- Stop renin–angiotensin system antagonists if the serum potassium concentration increases to 6.0mmol/L or more and other drugs known to promote hyperkalaemia have been discontinued.[10]

The Association of British Clinical Diabetologists (ABCD) and Renal Association published clinical guidelines: Hypertension management and renin-angiotensin-aldosterone system blockade in patients with diabetes, nephropathy and/or chronic kidney disease provide some guidance on the management of potassium to allow the safe use of RAAS inhibitors in patients with diabetes and CKD.[21]

Additional information: comparators

There are no established comparator medicines administered long-term to manage hyperkalaemia in patients with CKD, with or without heart failure, who require RAAS inhibitor therapy.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
Patiromer	8.4 g to 25.2g once daily	2,093 to 4,186

Costs from BNF online on 7 April 2020.

Additional information: budget impact

The submitting company estimated there would be 700 patients eligible for treatment with patiromer in each year. This figure was calculated using estimated figures for the prevalence of CKD stage 3-5 in Scotland, the proportion of these patients receiving RAAS inhibitor therapies and the percentage of patients receiving RAAS inhibitor therapies who experience a serum potassium level of >6.0 mmol/L. The estimated uptake rate was 19.5% (137 patients) in year 1 and 52.0% (364 patients) in year 5.

The gross impact on the medicines budget was estimated to be £275k in year 1 rising to £732k in year 5. As no medicines were assumed to be displaced the net medicines budget impact is equivalent to the gross impact.

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This assessment is based on data submitted by the applicant company up to and including 14 August 2020.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the

considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.