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Advising on new medicines for Scotland
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NHS SCOTLAND
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patiromer (as patiromer sorbitex calcium) 8.4g and 16.8g powder for oral suspension (Veltassa®) SMC2084

Vifor Fresenius Medical Care Renal Pharma UK Ltd

6 July 2018

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 NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

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

Chairman
Scottish Medicines Consortium

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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 which binds to potassium in the colonic lumen, reducing intestinal potassium reabsorption, increasing faecal potassium excretion, and 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) on stable doses of at least one renin-angiotensin-aldosterone system (RAAS) inhibitor treatment who develop hyperkalaemia.

The key clinical evidence for this indication is the OPAL-HK study, a multicentre phase III study comprising two phases: a single-arm, four-week treatment phase, followed by an eight-week, randomised-withdrawal phase.[3] 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.[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, and 16.8g / day in those with potassium concentration ≥5.5 to <6.5mmol/L. 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. 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.[3]

In the treatment phase of the study, the primary outcome was the mean change in serum potassium concentration from baseline to week four, based on central laboratory measurement, assessed in a modified intention-to-treat (ITT) population, 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 four was -1.01mmol/L (95% confidence interval [CI]: -1.07 to -0.95), p<0.001. 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.[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.[3]

Patients who entered the randomised-withdrawal phase were allocated 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.[3]

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 four, or to the earliest visit at which the patient's serum potassium (measured locally) was <3.8mmol/L or ≥5.5mmol/L (ie 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.[3]

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 subjects receiving placebo discontinued RAAS inhibitor treatment due to recurrent hyperkalaemia, compared with 5% of subjects treated with patiromer.[2] 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.[3]

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

Table 1: Primary and secondary outcomes from the randomised-withdrawal phase of the OPAL-HK study (ITT population).[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 AMETHYST-DN phase II study provides supporting evidence of patiromer efficacy over a treatment period of one year.[5] 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]

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. 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 patients with 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%).[5]

Summary of clinical effectiveness issues

There is no universal definition of hyperkalaemia, however a serum potassium concentration ≥5.5mmol/L is commonly used. Complications such as life-threatening cardiac electrophysiological disturbances (for example asystole, ventricular fibrillation) can arise. The incidence of complications escalates with increasing severity of hyperkalaemia; the rate of increase in serum potassium concentration is also a risk factor.[6]

Patients with 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 ACE inhibitors, or 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.[6] It is estimated that approximately 30% of patients attending specialist renal clinics with advanced CKD have concomitant hyperkalaemia. Strategies employed to manage hyperkalaemia in patients with CKD include dietary modification, use of sodium bicarbonate to correct metabolic acidosis, diuretics, and medication review to avoid medicines associated with hyperkalaemia.[7] Cation exchange resins sodium polystyrene sulfonate (Resonium A®) or calcium polystyrene sulfonate (Calcium Resonium®) are licensed for the treatment of hyperkalaemia in specific settings; however the European Medicines Agency (EMA) notes that there are limited prospective, long-term data on their use, 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]

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 concentration ≥5.5mmol/L in chronic heart failure, and ≥6.0mmol/L in CKD).[8, 9]

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.

The submitting company has requested that SMC considers patiromer when positioned for use in patients with stage 3 or 4 CKD on at least one RAAS inhibitor treatment who develop hyperkalaemia.

In the OPAL-HK study, in patients with hyperkalaemia, CKD and continuing on RAAS inhibitor treatment, the addition of patiromer reduced serum potassium concentrations by a mean of 1mmol/L after four weeks. Approximately three-quarters of patients achieved serum potassium concentrations in the normal range during this treatment phase. In the subgroup of patients with a baseline serum potassium concentration ≥5.5mmol/L who had responded to patiromer, the study demonstrated that ongoing treatment with the cation-exchange polymer maintained the reduction in serum potassium concentration, and was associated with a significantly lower proportion of patients with recurrent hyperkalaemia when 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 (ie serum potassium concentration >5.5mmol/L) developed in 15% of patiromer patients.

The study sample size was relatively small for a commonly encountered clinical scenario. This may be due to the choice of biochemical outcome. The study was 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.[2]

The OPAL-HK study provided evidence for the use of patiromer for up to 12 weeks of treatment. 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.[2, 5]

An enabling effect of patiromer on RAAS inhibitor prescription 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 (CV) 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 patients with chronic heart failure who were at risk of hyperkalaemia;[10] there are no data for patiromer facilitating the titration of ACE inhibitors or ARBs.

No patient-reported outcome data were collected.

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.[2]

Patients in the study received doses as high as 50.4g daily. 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.

The exclusion of some groups of patients from OPAL-HK, who may be considered to have a need for RAAS inhibition (eg those with recent cardiovascular events, and severe heart failure) reduces the generalisability of the study results to real-life practice. 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.

The summary of product characteristics 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.[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;[1] this may be challenging for patients with CKD who are likely to enounter 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 and may require oral supplementation.[1]

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing patiromer versus a no patiromer strategy in adult patients with stage 3 or 4 CKD who have developed hyperkalaemia whilst on RAAS inhibitor treatment. The comparator in the economic analysis was not clearly specified, but in both treatment arms patients could continue to receive RAAS inhibitor treatment. A Markov model with a monthly cycle length and a 35-year time horizon was used in which patients started in CKD stage 3 to 4 health state with a baseline age of 65 years and could transition to states consisting of CKD progression (stage 5 CKD or end-stage renal disease [ESRD]), hyperkalaemia (serum potassium ≥5.5mmol/L) resulting in hospitalisation, CV event (myocardial infarction [MI] or stroke) followed by post CV event, or straight to the CV event state, and death (from each state). In the model long term CKD and CV benefits from patiromer were primarily driven by the impact of facilitating RAAS inhibitor continuation from the management of hyperkalaemia.

The primary clinical data used in the economic analysis was post hoc analysis of the proportion of patients discontinuing RAAS inhibitor treatment over the randomised withdrawal phase of the OPAL-HK study, with the placebo arm representing the no patiromer comparator. The RAAS inhibitor discontinuation proportion due to hyperkalaemia at the end of the 8-week study was 5% for patiromer and 52% for placebo. Baseline monthly transition probabilities for placebo (no patiromer) were derived from a range of published sources. The relative risks of transitioning to CKD progression, CV event or hyperkalaemia states, or from each of these to death, associated with RAAS inhibitor continuation vs discontinuing RAAS inhibitor treatment were based on a Bayesian network meta-analysis of RCTs comparing CKD and CV outcomes for RAAS inhibitor therapies versus placebo in patients with CKD.[11] In addition, post hoc analysis of OPAL-HK study randomised-withdrawal phase data on hyperkalaemia outcomes was used to estimate the relative risk (RR) for the transition probability to the hyperkalaemia state (RR of 0.25) associated with hospitalisation and risk of a CV event or death. The proportion of patients experiencing RAAS inhibitor discontinuation in the placebo / no patiromer cohort was assumed to remain constant over the duration of the time horizon. Patiromer treatment was assumed to be of 7 years duration based on clinical expert opinion and typical life expectancy in stage 3 to 4 CKD patients. On cessation of patiromer it was assumed that a further 11% of patients would discontinue RAAS

inhibitor treatment based on an analysis of Clinical Practice Research Datalink (CPRD) UK observational data, and hence the RRs were adjusted to allow for this. Age related CKD mortality and all-cause mortality was included in the economic analysis.

Utility decrements from age adjusted UK population values for hyperkalaemia hospitalisation, CKD stage 3 to 4, CKD progression and CV events were derived from a variety of published sources using a range of utility elicitation methods including EQ 5D, and disutilities were also applied to specific patiromer adverse events.

Medicine acquisition costs, concomitant medicines, health state event, death in hospital costs, and adverse event resource use and costs were estimated based on multiple published sources. Health state costs were based on estimates for the proportion of patients experiencing an MI vs stroke, and proportions receiving peritoneal dialysis, haemodialysis and kidney transplant, and the risk and cost of MRSA infection whilst on dialysis. The cost of RAAS inhibitor was based on the mean dose of ACE inhibitors received by patients in the OPAL-HK study. The cost of patiromer was based on an assumption that a daily dose of 8.4g would be used.

A Patient Access Scheme (PAS) has been proposed by the submitting company and assessed by the Patient Access Scheme Assessment Group (PASAG) as being acceptable for implementation in NHSScotland. The base case results for patiromer were an incremental cost-effectiveness ratio (ICER) of £13,264 per quality adjusted life year (QALY). The key driver of incremental cost was the additional medicines cost for patiromer, with the primary cost offset and QALY gain associated with reduced CKD progression (ESRD) for patients receiving patiromer (via slowing of progression to CKD stage 5 from better RAAS inhibitor maintenance).

One way sensitivity analysis indicated the ICER was most sensitive to the relative risks with vs without RAAS inhibitor of transitioning to the CKD progression state (Table 2). Additional sensitivity analysis requested from the company demonstrated that the ICER was also sensitive to varying the RAAS inhibitor discontinuation proportion assumed for placebo/no patiromer (Table 2). Scenario analysis showed there was some sensitivity to increasing the post patiromer proportion of patients discontinuing RAAS inhibitor to be the same as in the placebo group, the maximum treatment duration for patiromer, and a time horizon ≤15 years, with ICERs around £20,000/QALY gained for each of these (Table 2).

Table 2: Key scenario analysis results

Sensitivity/Scenario analysis	**ICER (cost/QALY) with PAS**
95% CI bounds for CKD to CKD progression RR	dominant to £43,061
Increasing post-patiromer discontinuation rate from 11.3% to 49% (consistent with discontinuation in placebo arm OPAL-HK study)	£20,907
Reducing maximum patiromer treatment duration to 4 years (7 years in base case)	£4,624
Increasing maximum patiromer treatment duration to 12 years (7 years in base case)	£19,116
Assuming 2% annual decrease in RAAS inhibitor continuation with patiromer whilst on treatment	£15,142
Varying RAAS inhibitor continuation proportion for placebo ±10%	£5,958 - £24,723
Varying RAAS inhibitor continuation proportion for placebo ±20%	£651 - £48,597
Including non-responders to patiromer (56%)	£18,683
10-year time horizon	£19,572

Sensitivity/Scenario analysis	ICER (cost/QALY) with PAS
15-year time horizon	£13,291
5% patients receive maximum 25.2g daily dose patiromer (i.e. additional 8.2g sachet)	£15,249
CI = confidence interval, RR = relative risk, ESRD= End Stage Renal Disease, CKD = Chronic Kidney Disease	

There are several weaknesses and uncertainties with the economic analysis:

- There are limitations with the OPAL-HK study as a basis of the economic analysis, as it is of short duration, and based on endpoints that do not readily correlate with longer term CKD progression and CV related outcomes over a 35-year model time horizon. The analysis is dependent on the relationship with long term outcomes from post hoc analysis of RAAS inhibitor discontinuations and hyperkalaemia event data from the 8-week randomised-withdrawal phase of the OPAL-HK study and so is uncertain.
- In addition, the patiromer data used from the randomised-withdrawal part of the OPAL-HK study are in patients who are responders to patiromer, and hence likely to result in overestimated hyperkalaemia relative risk reduction and RAAS inhibitor continuation relative to clinical practice where a proportion of patients treated would be expected not to be responders to treatment. The company has provided an additional analysis in which the 56% of patients who did not respond in the treatment phase of OPAL-HK study were included in the model and assumed to experience the same risk of hyperkalaemia and CKD/CV events as placebo. This resulted in an ICER of £18,683/QALY with PAS.
- An important driver of cost offsets and QALY gains for patiromer is associated with RAAS inhibitor maintenance delaying progression to CKD stage 5/ESRD. Sensitivity analysis demonstrated that uncertainty in relative risks for CKD progression with vs without RAAS inhibitor could result in relatively high ICERs with PAS.
- In addition, there is uncertainty over the proportion of patients over time who would continue RAAS inhibitor treatment with placebo, with the ICER sensitive to varying this parameter
- It is likely that an assumed 2-week hospitalisation for patients in the hyperkalaemia state is too long for Scottish clinical practice. However, the results were not sensitive to reducing the length of stay.

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

Summary of patient and carer involvement

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

- We received a patient group submission from Kidney Research UK, which is a registered charity.
- Kidney Research UK has received 15.5% 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 serious 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.
- Patients with acute hyperkalaemia normally manage their condition with multiple treatments. Kidney patients are already taking multiple medications due to comorbidities and are often on dialysis due to end stage kidney failure. This adds to the overall burden of multiple 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 medications, such as RAAS inhibitors. Patients really struggle with most dietary measures, therefore adherence is a real issue and often impossible for many patients.

- A licensed medicine that would help patients control long-term raised potassium levels will ultimately offer hope to patients who have struggled to maintain an appropriate diet and may allow patients to receive more appropriate levels of RAAS inhibitors.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) document "SIGN 103 Diagnosis and management of chronic kidney disease", published in 2008, noted that hyperkalaemia (>5.5 mmol/L) is a recognised consequence of ACE inhibitor and ARB therapy and can occur independently at various stages of CKD. [12]Modest, stable hyperkalaemia may be preferable to discontinuing a useful treatment. In the absence of other recognised medical causes the patient's diet should be investigated for sources of potassium.

SIGN 147 "Management of chronic heart failure" (March 2016) also describes the expected biochemical disturbance associated with ACE inhibitors and / or ARB.[9] The guideline advises that if an increase in serum potassium concentration is small and asymptomatic, no action is necessary. Intervention (discontinuation of ACE inhibitor / ARB, and obtaining specialist advice) is recommended if potassium concentration increases to 5.5mmol/L.

The National Institute for Health and Care Excellence guideline 182 "Chronic kidney disease in adults: assessment and management" (January 2015) makes the following relevant recommendations:[8]

- In people with CKD, measure serum potassium concentrations and estimate the GFR before starting RAAS inhibitors. Repeat these measurements between one and two weeks after starting RAAS inhibitor and after each dose increase.
- 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 RAAS inhibitors, 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 RAAS inhibitors, but be aware that more frequent monitoring of serum potassium concentration may be required.
- Stop RAAS inhibitors if the serum potassium concentration increases to 6.0mmol/L or more and other drugs known to promote hyperkalaemia have been discontinued.[8]

The Renal Association published guidance in July 2017, "Hypertension management and renin-angiotensin-aldosterone system blockade in patients with diabetes, nephropathy and/or chronic kidney disease".[7] Hyperkalaemia is common in patients with diabetes and CKD. It is very common (greater than 30%) in patients who have advanced CKD who are managed in the renal clinics. The cause of such hyperkalaemia can be multifactorial, including renal failure, type IV renal tubular acidosis, diet and drugs. Hyperkalaemia limits the use of RAAS inhibitors. Chronically high potassium levels have traditionally been controlled with restricted diet, diuretics and avoiding drugs that cause hyperkalaemia. Sodium bicarbonate (500mg twice daily) is an option in patients with hyperkalaemia and where bicarbonate is less than 22mmol/L. Larger doses of sodium bicarbonate can be used but often require a concomitant increase or addition of a loop diuretic dose.

New potassium binding agents have been tested for safety and efficacy in randomised controlled trials for management of chronic hyperkalaemia in patients with CKD. In 306 patients with diabetes and CKD stages 3 and 4 who were treated with RAAS blockade (an ACEI or ARB with or without spironolactone), the use of patiromer was associated with a significant and sustained decrease in serum potassium over 52 weeks. In a study of 237 patients with CKD, patiromer was able to reduce serum potassium by 1mmol/L over 4 weeks. In another study of 243 patients (more than 50% of whom had diabetes) the potassium binder achieved an approximately 1 mmol/L reduction in serum potassium over 4 weeks in patients with and without heart failure. The treatment with patiromer was associated with decreased aldosterone levels and decreased blood pressure, which may provide additional benefits. The guideline notes that the studies were of short duration and the possible ACE inhibitor or ARB use facilitated with potassium binders has not been shown to improve cardiovascular events or mortality. In future, patiromer may be very useful in treating patients with diabetes and CKD, particularly when it is associated with left ventricular dysfunction.[7]

Additional information: comparators

There are no established comparator treatments for treatment of hyperkalaemia in patients with CKD and RAAS inhibitor treatment.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
patiromer	**8.4g to 25.2g orally once daily**	**3,640 to 7,280**

Doses are for general comparison and do not imply therapeutic equivalence. Costs from www.mims.co.uk on 07 May 2018. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 19,176 patients eligible for treatment with patiromer in year 1, rising to 19,435 patients in year 5. The estimated uptake rate was 1.6% in year 1 rising to 8.4% in year 5. The company estimated 306 patients would be treated in year 1, rising to 1,631 patients treated in year 5.

Without PAS:
The gross impact on the medicines budget was estimated to be £1.01million in year 1 rising to £4.86million in year 5.

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This assessment is based on data submitted by the applicant company up to and including 15 June 2018.

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 drug 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.