National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Patiromer for treating hyperkalaemia

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Vifor Fresenius Medical Care Renal Pharma UK	Yes this is an unmet clinical need and is thus appropriate for NICE appraisal.	Comment noted.
	Kidney Care UK	Yes	Comment noted.
	Renal Association (endorsed by Royal College of Physicians)	Yes – this is a relatively new field of therapy but does remain niche to certain medical areas. Therapies directed at augmenting GI potassium excretion In the form of resonium has been around for years, it has been unreliable in the acute setting. Lepage L, Dufour AC, Doiron J, Handfield K, Desforges K, Bell R, Vallée M, Savoie M, Perreault S, Laurin LP, Pichette V, Lafrance JP: Randomized clinical trial of sodium polystyrene sulfonate for the treatment of mild hyperkalemia in CKD. Clin J Am Soc Nephrol 10: 2136–2142, 2015 Data on the chronic management might support its use. Despite this there is an unmet need in this field of hyperkalaemia to assist in optimal patient care, the estimation varies with a recent “real world” study use of ACE-I and ARB, suggesting an overall very low rate (<2%) of even mild	Comment noted.

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		forms of hyperkalemia (eg, >5 mmol/L), suggesting that the vast majority of persons prescribed these medications can be considered low-risk.	
Wording	Vifor Fresenius Medical Care Renal Pharma UK	It is our belief that the remit should be to appraise the clinical and cost effectiveness of Veltassa® (patiromer) in **treating hyperkalaemia in adult patients with Chronic Kidney Disease 3/4 (CKD) and Chronic Heart Failure (CHF) who develop hyperkalaemia (HK) on Renin-Angiotensin-Aldosterone System inhibitors (RAASi) therapies.** While there are compelling data and clinical practice guidelines supporting the use of RAASi to reduce adverse cardiovascular and renal outcomes in certain high-risk patient populations [KDIGO, 2012; ESC 2016; NICE 2010, NICE 2014], these medications are contraindicated in patients with high serum potassium levels [Yancy, 2013; Ponikowski, ESC Web Addenda 2016]. Adherence to these guidelines is often poor [Rassi, 2013; Komajda 2016; Maggioni, 2013; Philipneri, 2008; Tuot, 2012], and the risk of hyperkalaemia is a major barrier for failure to start these drugs in patients who are indicated to receive them [Yildirim, 2012]. As such, use of RAASi in CKD and HF patients can be limited due to the increased risk of acute hyperkalaemia with accompanying risks of cardiac arrhythmia and death [Albert, 2009; McMurray, 2012; KDOQI, 2007; Pappoe, 2010; Yildirim, 2012]. Moreover, the occurrence of hyperkalaemia or anticipation of developing hyperkalaemia with RAASi medications leads to dose reduction or discontinuation, thus leaving patients at increased cardiovascular and/or renal risk [Pitt, 2015; Epstein 2015]. The availability of a well-tolerated and efficacious medicinal product that has been thoroughly studied in patients prescribed RAAS inhibitors and reliably lowers elevated serum potassium, would allow physicians to maximize RAASi therapy in their patients who will derive the most benefit from them i.e. those who are at increased risk for developing hyperkalaemia (e.g., HF, CKD). For this reason we believe the potential of patiromer to enable and maintain	Comment noted. The remit is usually kept broad and reflects the marketing authorisation and anticipated marketing authorisation. The population in the scope has been amended to focus on the patients in whom patiromer would be used.

<table>
<tr><th>Section</th><th>Consultee/ Commentator</th><th>Comments [sic]</th><th>Action</th></tr>
<tr><td></td><td></td><td>concomitant RAAS inhibitor treatment should also form part of this assessment.</td><td></td></tr>
<tr><td></td><td>AstraZeneca UK</td><td>Yes</td><td>Comment noted.</td></tr>
<tr><td></td><td>Renal Association (endorsed by Royal College of Physicians)</td><td>I would adjust the wording to consider drug X for the treatment and prevention of acute and chronic hyperkalaemia. The reason for this is based on the data published and potential clinical need for a drug of this class and therapeutic intervention.</td><td>Comment noted. Patiromer does not have marketing authorisation for preventing hyperkalaemia. Both acute and chronic hyperkalaemia are covered in the present wording that reflects the marketing authorisation.</td></tr>
<tr><td>Timing Issues</td><td>Vifor Fresenius Medical Care Renal Pharma UK</td><td>A retrospective cohort and case-control analysis using patient data from the Clinical Practice Research Datalink (CPRD) UK database and the Hospital Episode Statistics (HES) database in England reported the overall incidence of a first hyperkalaemic event (serum K+ ≥5.0 mEq/L) as 2.86 per 100 patient-years in patients seeking healthcare services in England.(1) Of patients with CKD and a recorded hyperkalaemic event (N=34,912), 6.5% had CHF, 59.2% were taking RAAS inhibitors and 9.9% had previous exposure to RAAS inhibitors.(2)

Table 1: Incident cases of hyperkalaemia in England(28)
<table>
<tr><th></th><th>Incident cases of hyperkalaemia, n (%)</th><th>Incidence of initial hyperkalaemic event per 100 patient-years (95% CI)</th></tr>
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</td><td>Comment noted.</td></tr>
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		Overall	195,178 (100.0)	2.86 (2.83, 2.89)
		Severity of hyperkalaemic event		
		K^+ 5.0–≤5.5	177,945 (91.2)	2.61 (2.58, 2.63)
		K^+ >5.5–≤6.0	14,020 (7.2)	0.21 (0.20, 0.21)
		K^+ >6.0	3213 (1.6)	0.05 (0.04, 0.05)

UK guidelines for the management of hyperkalaemia currently focus only on the management of acute elevations of K^+ levels.(3,4) Although acute management of hyperkalaemia stabilises K^+ concentrations, the long-term management is not addressed and remains a significant unmet medical need.

Long-term strategies for managing patients with hyperkalaemia are based on clinical judgement, options are limited and are fundamentally different from those in the acute setting. The cation exchange resins, sodium polystyrene sulphonate [SPS; Kayexalate®] and calcium polystyrene sulphonate [CPS; Sorbisterit®] are known to lower K^+ levels in the acute setting, however, their transient effect on serum K^+, lack of long-term data, risk of serious gastrointestinal adverse events (AEs) and sodium load precautions prevent their use for the management of chronic hyperkalaemia.

Given the limitations of treatment with the cation exchange resins, diuretics and sodium bicarbonate, treatment options for persistent hyperkalaemia have been limited to low K^+ diet and modification of hyperkalaemia-inducing medications, such as RAAS inhibitors (RAASi).
In patients receiving RAASi, the most common strategy for long-term management of hyperkalaemia is RAAS inhibitor dose reduction or RAAS inhibitor discontinuation.

Furthermore, UK guidelines recommend non initiation of RAAS inhibitors in cases where serum K+ is >5 mEq/L.(5)

Importantly, in patients with CKD and CHF, RAAS inhibitors are commonly prescribed yet real world data shows that 47% of patients discontinue or receive submaximal doses (6). This situation therefore creates a clinical

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		dilemma as RAAS inhibition is a globally accepted management approach with demonstrably significant clinical benefits that patients with RAAS inhibitor dose reduction and dose discontinuation are deprived of and pharmacoeconomic benefits that the health service and the tax payer are deprived of. (7-10,15) These benefits include: significant reductions in progression of CKD; fewer cardiovascular events; reduced mortality, morbidity and hospitalisation for CHF and lower rates of post-myocardial infarctions (11-14) This thus highlights a clinically significant unmet need that can and should be addressed speedily for the benefit of patients and the NHS as a whole. It is important that physicians are aware at the time of prescription that patiromer effectively treats hyperkalaemia to enable RAASi, which is of paramount importance for patient care. **REFERENCES** 1.Smith DH, Raebel MA, Chan KA, Johnson ES, Petrik AF, Weiss JR, et al. An economic evaluation of a laboratory monitoring program for renin-angiotensin system agents. Medical decision making : an international journal of the Society for Medical Decision Making. 2011;31(2):315-24. 2.Xie X, Liu Y, Perkovic V, Li X, Ninomiya T, Hou W, et al. Renin-Angiotensin System Inhibitors and Kidney and Cardiovascular Outcomes in Patients With CKD: A Bayesian Network Meta-analysis of Randomized Clinical Trials. Am J Kidney Dis. 2016;67(5):728-41 3.National Institute for Health and Clinical Excellence. British National Formulary. 9: Nutrition and blood. 2017. 4.UK Renal Association. Clinical Practice Guidelines: Treatment of Acute Hyperkalaemia in Adults. 2014 March 2014. 5.National Institute for Health and Clinical Excellence. Chronic kidney disease in adults: assessment and management. 2014.	

Section	Consultee/ Commentator	Comments [sic]	Action
		6.Epstein M, Reaven NL, Funk SE, McGaughey KJ, Oestreicher N, Knispel J. Evaluation of the treatment gap between clinical guidelines and the utilization of renin-angiotensin-aldosterone system inhibitors. The American journal of managed care. 2015;21(11 Suppl):S212-20. 7.The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. . The New England journal of medicine. 1992;327(10):685-91. 8.Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. The New England journal of medicine. 2001;345(12):861-9. 9.Hou FF, Zhang X, Zhang GH, Xie D, Chen PY, Zhang WR, et al. Efficacy and safety of benazepril for advanced chronic renal insufficiency. The New England journal of medicine. 2006;354(2):131-40. 10.Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. The New England journal of medicine. 1999;341(10):709-17. 11.van Vark LC, Bertrand M, Akkerhuis KM, Brugts JJ, Fox K, Mourad JJ, et al. Angiotensin-converting enzyme inhibitors reduce mortality in hypertension: a meta-analysis of randomized clinical trials of renin-angiotensin-aldosterone system inhibitors involving 158,998 patients. European heart journal. 2012;33(16):2088-97. 12.Orsborne C, Chaggar PS, Shaw SM, Williams SG. The renin-angiotensin-aldosterone system in heart failure for the non-specialist: the past, the present and the future. Postgraduate medical journal. 2017;93(1095):29-37. 13.Packer M, Poole-Wilson PA, Armstrong PW, Cleland JG, Horowitz JD, Massie BM, et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality	

Section	Consultee/ Commentator	Comments [sic]	Action
		in chronic heart failure. ATLAS Study Group. Circulation. 1999;100(23):2312-8. 14.Xie X, Liu Y, Perkovic V, Li X, Ninomiya T, Hou W, et al. Renin-Angiotensin System Inhibitors and Kidney and Cardiovascular Outcomes in Patients With CKD: A Bayesian Network Meta-analysis of Randomized Clinical Trials. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2016;67(5):728-41. 15.Reimar W. Thomsen, Sia K. Nicolaisen, Pa˚l Hasvold, Ricardo Garcia Sanchez, Lars Pedersen, Kasper Adelborg, Kenneth Egstrup, Martin Egfjord and Henrik Toft Sørensen. Elevated potassium levels in patients with chronic kidney disease: occurrence, risk factors and clinical outcomes—a Danish population-based cohort study. Nephrol Dial Transplant (2017) 1–10	
	Renal Association (endorsed by Royal College of Physicians)	The appropriate deliberation should be given to this therapy area, It must be recognised that a further molecule, which is somewhat different is also undergoing evaluation in clinical studies – NICE may therefore wish to consider an evaluation of the area when this molecule is available. There is some urgency but I would summarise that timing is perhaps not critical.	Comment noted.
Additional comments on the draft remit	Vifor Fresenius Medical Care Renal Pharma UK	To re-iterate, the importance of patiromer for patients with CKD 3/4 and CHF commonly treated with RAAS inhibitors, real world data shows that 47% of patients discontinue or receive submaximal doses (6). This situation therefore creates a clinical dilemma as RAAS inhibition is a globally accepted management approach with demonstrably significant clinical and pharmacoeconomic benefits that patients with RAAS inhibitor dose reduction and dose discontinuation are deprived of. (7-10) The health service and the tax payer are also deprived of potential pharmacoeconomic benefits, because the use of existing therapies such as SPS/CPS in the acute setting does not allow for the long-term treatment of hyperkalaemia. It is therefore important that patiromer is not viewed as an acute alternative for SPS/CPS. Instead, patiromer is addressing a significant unmet need in the long-term management of such patients.	Comment noted. Comparators have been amended to reflect the clinical use. In addition, subgroups have been added to the scope.

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		Patiromer enables patients with CKD 3 /4 and CHF to maintain patients normokalaemic which allows them to benefit from their required “disease-modifying and life-saving” RAASi therapy in the long-term. Thus, the potential to use patiromer in patients with the risk of developing recurrent hyperkalaemia on RAASi therapies is essential and addresses an unmet medical need as illustrated in OPAL-HK (see below). The ability of patiromer to enable concomitant RAAS inhibitor treatment was assessed in part B of the OPAL-HK study – a multinational, single blind, two-phased study investigating the safety and efficacy of patiromer in patients with CKD who were receiving at least one RAAS inhibitor and who also had hypertension and hyperkalaemia. Fifty two percent (52%) of subjects receiving placebo discontinued RAAS inhibitor treatment because of recurrent hyperkalaemia compared with 5% of subjects treated with patiromer. (16) The ability of patiromer to enable concomitant spironolactone treatment was also investigated in a randomised, double-blind, placebo-controlled study in heart failure patients who were clinically indicated to receive Aldosterone Antagonists. Among CHF patients at risk of elevated serum potassium, a higher proportion of patients were able to use a higher dose of spironolactone with patiromer (91%) vs placebo (74%) at the end of treatment (p=0.019). (17) Patiromer is therefore a potentially important treatment that offers patients the ability to benefit from the renal and cardio-protective characteristics of RAASi treatments. **REFERENCES** 16.Vifor Fresenius Medical Care. Veltassa - EU summary of product characteristics. 2017. 17.Pitt B, Bakris GL, Bushinsky DA, Garza D, Mayo MR, Stasiv Y, et al. Effect of patiromer on reducing serum potassium and preventing recurrent hyperkalaemia in patients with heart failure and chronic kidney disease on RAAS inhibitors. European journal of heart failure. 2015;17(10):1057-65.	

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Vifor Fresenius Medical Care Renal Pharma UK	The European Resuscitation Council's definition of mild, moderate, and severe hyperkalaemia as quoted in the draft scope is more suited for the management of hyperkalaemia in emergency settings and thus may not be the most appropriate for the assessment of patiromer. In the patiromer studies and CE model, the ranges for hyperkalaemia were based on the references below [1,2,3] and defined as: **Mild >5.0 to ≥5.5 mmol/L** **Moderate from >5.5 to ≥ 6.0 mmol/L** **Severe > 6.0 mmol/L** **REFERENCES** 1. Rastegar A, et al. Postgrad Med J. 2001;77:759–64; 2. Einhorn LM, et al. Arch Intern Med. 2009;169:1156–62; 3. Kovesdy CP. Am J Med. 2015;128:1281–7] The treatment options for recurrent or chronic hyperkalaemia (moderate or severe), due to CKD or the use of drugs that inhibit the RAAS (RAASi) include diet adaptation, use of diuretics, treatment of chronic metabolic acidosis, and avoidance of those medicines causing hyperkalaemia (e.g. non-steroidal anti-inflammatories, RAASi). With regards to the latter, one should consider the medium to long-term implications of stopping these potentially 'disease-modifying and life-saving' drugs on clinical outcomes. With regards to further options such as SPS and CPS which reduce potassium levels in the body, the following should be noted: i) treatment has to be stopped when potassium is <5.0 mmol/L because of the risk of hypokalaemia ii) data on the safety and efficacy of mid to long-term use for the management of hyperkalaemia are lacking for these drugs	Comment noted. The reason for digressing from the standard definition, should be explained in the company's submission. The background section has been updated to include reference to NICE clinical guideline 108.

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		Additionally, in support of the importance of potassium monitoring in Heart Failure (HF) patients with CKD, we suggest the consideration of NICE Clinical Guideline 108 which recommends that in patients with heart failure due to left ventricular systolic dysfunction who are taking aldosterone antagonists and/or ARBs, potassium, creatinine levels, and eGFR should be closely monitored. Specialist advice should also be sought if the patient develops hyperkalaemia or renal function deteriorates.	
	AstraZeneca UK	*NICE text: The risk of hyperkalaemia is increased further by medicines such as potassium supplements, inhibitors of renin–angiotensin–aldosterone system...* Suggestion to include: "including mineralocorticoid receptor antagonists (MRAs)" Please note spironolactone is contraindicated in patients with serum potassium level > 5.0 mmol/L at initiation. Furthermore, in heart failure patients in Europe, from the 5.6% and 3.1% patients in whom a MRA is contraindicated or not tolerated, 35.1% and 36.1% of those are due to hyperkalaemia respectively Maggioni, A.P., et al., *Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12,440 patients of the ESC Heart Failure Long-Term Registry.* Eur J Heart Fail, 2013. **15**(10): p. 1173-84 *NICE text: Relevant guidelines:* Suggestion to include: reference to the 2016 ESC HF guidelines • ACE-I / ARB should be stopped and specialist advice sought if potassium rises >5.5 mmol/L • When using MRAs, caution/seek specialist advice in the case of 'significant hyperkalaemia' (>5.0 mmol/L). • Monitor if K+ rises above 5.5 mmol/L; stop MRA immediately and seek specialist advice if K+ rises to >6.0 mmol/L	Comment noted. Mineralocorticoid receptor antagonists (MRAs) are also known as aldosterone receptor inhibitors and covered under the definition of renin–angiotensin–aldosterone system inhibitors. No change required. Comment noted. The background section has been updated to include reference to NICE clinical guideline 108 'Chronic heart failure in adults: management' that recommends closely monitoring potassium, creatinine levels, and estimated

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		• Triple combination of an ACE-Is, ARB and MRA is NOT recommended *https://www.escardio.org/static_file/Escardio/Guidelines/ehw128_Addenda.pdf* Suggestion to include: reference to the Renal Association guidelines • Do not routinely start ACE inhibitors or ARBs if K > 5 mmol/L) • If K+ rises >6 consider repeating, stop drugs that may contribute to rise, (NSAIDs, potassium-retaining diuretics, trimethoprim etc) https://renal.org/information-resources/the-uk-eckd-guide/hypertension/	glomerular filtration rate (eGFR) in people with heart failure due to left ventricular systolic dysfunction who are taking aldosterone antagonists and/or ARBs and specialist advice, if the patient develops hyperkalaemia or renal function deteriorates. The background section is intended to briefly present the disease, epidemiology and current treatment options. Detailed description of all relevant national and international guidelines could be included in the consultees' submission.
	Renal Association (endorsed by	The background is extremely brief. The quoted mention acute and prevention of hyperkalaemia – hence the change in wording as above. It also discusses dialysis which is important. The main issue I have is the disconnect with the	Comment noted. The background section is intended to briefly describe the disease,

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	Royal College of Physicians)	scope and background. The background should be more detailed to cover the revised scope.	epidemiology and current treatment options. Patiromer does not have marketing authorisation for prevention of hyperkalaemia and it is not intended to be used in acute setting.
The technology/ intervention	Vifor Fresenius Medical Care Renal Pharma UK	Patiromer (Veltassa®) is indicated for adults in treatment of hyperkalaemia. It is a new active substance, a novel, next-generation, non-absorbed, sodium-free, cross-linked polymer that binds excess K+ in the distal colon. [1, 2]. Furthermore, patiromer also keeps the potassium levels within normal levels over time and enables optimization of the renal- and cardio-protective RAASi treatment [1, 3-5] Patiromer binds potassium, in exchange for calcium, as it moves through the gastrointestinal tract. The primary site of action of patiromer is the distal colon, where concentrations of free potassium are highest. The binding in the gastrointestinal tract prevents reabsorption into the systemic circulation and enhances faecal potassium excretion [6]. The binding of potassium in the gastrointestinal lumen thus reduces the concentration of free potassium, resulting in a reduction of serum K+ levels [7]. The use of calcium rather than sodium as exchange counterion is a desirable characteristic for patients who cannot tolerate even small increases in sodium load, such as patients with HF, hypertension or at risk of oedema, all of which are common in patients with CKD [6, 8-9]. The safety and efficacy of patiromer has been demonstrated consistently in several studies, including those of long-term and short-term duration which enrolled populations enriched with conditions that predispose patients to	Comment noted. No changes required.

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		hyperkalaemia: CKD, HF, diabetes, and use of RAASi agents, and who presented with a range of starting serum potassium values. The two pivotal trials were the following: 1) Phase III OPAL-HK study, which evaluated patiromer treatment in hyperkalaemic patients with CKD who were taking RAAS inhibitors. [5] 2) Phase II AMETHYST-DN trial, which evaluated the use of patiromer over 52 weeks in hyperkalaemic patients with CKD and type 2 diabetes who were taking RAAS inhibitors. [3] **REFERENCES** 1.Vifor Fresenius Medical Care, Veltassa - EU summary of product characteristics. 2017. 2.European Medicines Agency (EMA). Veltassa: EPAR - Public Assessment Report. 2017; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004180/WC500232691.pdf 3.Bakris, G.L., et al., Effect of Patiromer on Serum Potassium Level in Patients With Hyperkalemia and Diabetic Kidney Disease: The AMETHYST-DN Randomized Clinical Trial. Jama, 2015. 314(2): p. 151-61. 4.Pitt, B., et al., Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo controlled study in patients with chronic heart failure (the PEARL-HF trial). European Heart Journal, 2011. 32: p. 820-828. 5.Weir, M.R., et al., Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. N Engl J Med, 2015. 372: p. 211-221. 6.Chaitman, M., D. Dixit, and M.B. Bridgeman, Potassium-Binding Agents for the Clinical Management of Hyperkalemia. P&T, 2016. 41(1): p. 43-50. 7.U.S. Food and Drug Administration VELTASSA (patiromer) for oral suspension: Prescribing information. 2015.	

Section	Consultee/ Commentator	Comments [sic]	Action
		8.Li, L., et al., Mechanism of Action and Pharmacology of Patiromer, a Nonabsorbed Cross-Linked Polymer That Lowers Serum Potassium Concentration in Patients With Hyperkalemia. J Cardiovasc Pharmacol Ther, 2016. 21(5): p. 456-65. 9.Weir, M.R., et al., Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. N Engl J Med, 2015. 372(3): p. 211-21.	
	Renal Association	Yes a fair synopsis of drug. It might be useful to add the frequency of administration and number of tablets on average to give a practical aspect of potential adherence	Comment noted. We do not include detailed posology in the scope.
Population	Vifor Fresenius Medical Care Renal Pharma UK	The population described in the scope is in line with the licensed indication. However the subgroup we plan to focus on in the submission is the population that we have modelled: Adults patients with CKD 3/4 and CHF who develop hyperkalaemia on RAASi therapies. Please also note that our intention is not to cover the emergency treatment of life-threatening hyperkalaemia due to our onset of action which occurs 4-7 hours after administration [1] and the availability of other well established acute interventions. REFERENCES 1.Vifor Fresenius Medical Care, Veltassa - EU summary of product characteristics. 2017	Comment noted. The scope has been updated to amend the population.
	AstraZeneca UK	Yes	Comment noted.
	Kidney Care UK	People with acute kidney injury could be considered separately as they may not be completely represented or covered in the other groups mentioned. We suggest further clarity be given to 'people with CKD' e.g. what stage of CKD, whether on dialysis or transplanted.	Thank you for your comment. Following the scoping workshop, the population has been broadened to people

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			with adults with hyperkalaemia. In addition, we have broadened the subgroups of people that should be considered.
	Renal Association (endorsed by Royal College of Physicians)	I would add the following 1. Elderly 2. Patients with AKI 3. Dialysis patients 4. Kidney transplants – could be combined in CKD patients 5. Patients on beta blockers 6. Patients post myocardial infarction 7. sacubitril valsartan use	Following the scoping workshop, the population has been broadened to people with adults with hyperkalaemia. In addition, we have broadened the subgroups of people that should be considered.
Comparators	Vifor Fresenius Medical Care Renal Pharma UK	There is currently no appropriate pharmacological comparator for the long-term treatment of recurrent hyperkalaemia in adults. In consultation with the Regulatory Authorities, it was agreed that the pivotal study OPAL-HK would not include an active comparator for ethical and clinical practice reasons. As stated in the European Public Assessment Report for patiromer, SPS and CPS don´t serve as a treatment option for long-term management of hyperkalaemia.[1] In today's NHS a variety of measures are used to manage hyperkalaemia clinically, including discontinuation of hyperkalaemia-inducing drugs such as RAAS inhibitors, diuretics, diet change (associated with significant compliance challenges), bicarbonates and potassium (K+) binders. Of	Comment noted. The comparators have been amended to take out reference to pharmacological treatments.

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		existing K+ binders, calcium polystyrene sulphonate (CPS) was accepted for use for the treatment of hyperkalaemia in patients with acute and chronic renal insufficiency, including patients undergoing dialysis treatment. However, there is insufficient clinical trial evidence for mid- to long-term hyperkalaemia treatment, or for maintaining hyperkalaemic patients on RAAS inhibitor therapy with CPS. There are limited prospective, long-term clinical trial data available to understand the safety and efficacy of these agents. These products are not well tolerated and their use can be associated with life-threatening side effects including intestinal necrosis. These issues make the administration of CPS for prolonged durations of time difficult. Additionally, CPS is contraindicated for treating patients with a serum potassium < 5.0 mmol/L and requires frequent stop and start cycles of drug administration, further complicating chronic dosing. Thus, there is a need for new therapeutics for hyperkalaemia whose efficacy and safety are well characterized and can be administered long term. Currently no treatment is available to CKD + CHF patients with hyperkalaemia who are also receiving RAAS inhibitors that: i) protects from recurring life-threatening hyperkalaemia and ii) enables long-term, guideline recommended RAAS inhibitor therapy and consequent improved treatment outcomes. Therefore, in patients receiving RAAS inhibitors who develop hyperkalaemia, the most common strategy for management of chronic hyperkalaemia is RAAS inhibitor dose reduction or discontinuation. Given the many limitations of the current therapies/strategies for long-term management of hyperkalaemia, patiromer offers an innovative solution in the described population and will serve as an important treatment in enabling the renal and cardio-protective benefits of RAASi treatments. REFERENCES	

Section	Consultee/ Commentator	Comments [sic]	Action
		1.European Medicines Agency (EMA). Veltassa: EPAR - Public Assessment Report. 2017; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004180/WC500232691.pdf	
	AstraZeneca UK	Yes. Although clinical management in the acute setting may include: calcium gluconate, salbutamol, insulin/dextrose etc. these are not appropriate comparators due to the speed of onset of patiromer. Best alternative care is likely a change in diet and either stopping medicines that cause hyperkalaemia, or treatment with sodium/calcium polystyrene sulphonate.	Comment noted.
	Renal Association (endorsed by Royal College of Physicians)	This covers the main comparators, at this stage for acute severe hyperkalaemia I would estimate it would be an add on therapy to current rather than alternative therapy	Comment noted.
Outcomes	Vifor Fresenius Medical Care Renal Pharma UK	• *Serum potassium level:* Yes, relevant to include. • *Episodes of severe hyperkalaemia (serum potassium level 6.5 mmol/L or above)* : No. There is limited experience in patients with serum potassium concentrations greater than 6.5 mmol/L. Vifor thus recommends the following as a replacement: - **Long-term treatment of hyperkalaemia** **5.1 - 6.5mmol/L** • *Cardiac arrhythmia*: No. This outcome is mainly applicable in the emergency setting and was not included as an outcome measure in our clinical programme.	Comment noted. The outcomes have been updated to include use of renin–angiotensin–aldosterone system inhibitor therapy.

Section	Consultee/ Commentator	Comments [sic]	Action
		• *Overall survival*: No. Vifor has not generated data on this outcome measure with patiromer, however the benefits of continued RAASi treatments have been well documented and will be included in the submission. • *Adverse effects of treatment:* Yes, this is relevant to include. • *Health related quality data*: Yes. Vifor has not generated data on this topic with patiromer specifically, however the benefits of continued RAASi treatments have been well documented and will be included in the submission. • Other potential outcomes to include: - Time to RAAS inhibitor discontinuation - Proportion of patients receiving any dose of RAAS inhibitor - Proportion of patients requiring an intervention (including RAAS inhibitor dose reduction or discontinuation) due to hyperkalaemia	
	AstraZeneca UK	Also include: - Time to normokalaemia - Optimised RAASi therapy use Please remove: Cardiac arrhythmia: based on available evidence in the clinical trials, this outcome is not appropriate. Although the mode of death in these patients is likely cardiac arrhythmia (brady or tachy-arrhythmias), definitive documentation of cause of death is challenging. - For modelling purposes, it may be more appropriate to include MACE, or 'fatal and non-fatal cardiac events'	Comment noted. The outcomes have been updated to include use of renin–angiotensin–aldosterone system inhibitor therapy.
	Renal Association (endorsed by	I am not clear on the potassium level – does this mean steady state level or after a certain number od days of therapy	Comment noted. The outcomes have been updated to include use

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	Royal College of Physicians)	In addition I would record episodes of moderate hyperkalaemia (6.0-6.4) as these levels precipitate a visit to the emergency department for a further blood test and possible intervention and reduction of these would have a significant health gain for the patient and economic gain for the NHS. Some data on the ability to relax dietary restrictions and thus allow consumption of "healthier foods may be useful but I am not sure easily measurable (it might be captured in the health related quality of life assessment). I would record cardiovascular death separately.	of renin–angiotensin–aldosterone system inhibitor therapy. Hospitalisations would captured in the economic modelling
Economic analysis	Vifor Fresenius Medical Care Renal Pharma UK	The purpose of this economic evaluation, in alignment with the clinical evidence and position from the Vifor Pharma Group, aims to explore the potential economic gains in patients for CKD with RAASi-enabling patiromer. The patient group analysed in the base case will be derived from the OPAL-HK trial, which incorporates patients at high risk of HK with CKD stage 3-4 on RAASi (Weir et al). This should allow the following subgroups to be considered: • patients with chronic kidney disease (CKD stage 3/4) • patients with heart failure (40% of OPAL-HK population) • patients on renin–angiotensin–aldosterone system inhibitors As stated previously, Veltassa® (patiromer) is currently under evaluation for patients at risk of HK and demonstrates potential benefits in maintaining patients on RAASi medications. At the end of the OPAL HK trial, patients in both the "patiromer" and "no patiromer" arms are distributed into a Markov model as for those who either continue on RAASi treatment or discontinue RAASi treatment. The perspective of this analysis takes on the viewpoint of the National Health Service (NHS) in England as is required and measures outcomes related to direct health costs, survival (i.e. life years gained) and quality-adjusted life years (QALYs) discounted at 3.5%.	Comment noted.

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		A non-systematic review of economic evaluations of patients with CKD on RAASi informed the design of the patiromer cost-effectiveness model. A Markov model with monthly cycles that include CKD health states (e.g. CKD, end-stage renal disease, death) in combination with cardiovascular outcomes (e.g. MI, stroke) as well as hyperkalemic events, was developed in Microsoft Excel 2016 ® (Redmond, WA). The addition of cardiovascular events and hyperkalemia in the model were included from clinicial expert feedback. The model simulates a maximum potential life-long time horizon. Although the duration of the time horizon is 35 years (maximum age 100 years old), the mean life span of individuals in the model (8.2) is comparable to real world evidence (average 7 thru 8 years).(16)	
	AstraZeneca UK	None	Response noted
	Renal Association (endorsed by Royal College of Physicians)	This in vague but I am not a health economist	Comment noted.
Equality and Diversity	Vifor Fresenius Medical Care Renal Pharma UK	To the best of our knowledge no changes are necessary.	Comment noted.
	AstraZeneca UK	None	Response noted
	Kidney Care UK	No comments.	Response noted

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	Renal Association (endorsed by Royal College of Physicians)	See comments above. No major omissions. The area is generic in scope to the needs of any patient with hyperkalaemia who might be eligible for this therapy based on the current SPMC. No groups to my understanding are excluded from potential therapy. Other areas of potential use and study have been detailed in the final section in those groups which may not be covered by this application but may benefit – I have added references.	Comment noted
Other considerations	Vifor Fresenius Medical Care Renal Pharma UK	n/a	Response noted
	AstraZeneca UK	We question whether the subgroup for T2D patients is appropriate as there is no known pathophysiological mechanism or drug used for the treatment of diabetes that is recognised to cause hyperkalaemia. Patients at risk of hyperkalaemia are likely to have CKD or HF, and be on treatments mentioned above.	Comment noted. The subgroup for diabetes mellitus has been removed.
	Renal Association (endorsed by Royal College of Physicians)	**I** am sure the aspect of tolerability will be discussed so that an idea of adherence to therapy is available to assess. I realise that guidance will only be issued according to market authorisation but broader consideration should be evaluated.	Comment noted. Tolerability of patiromer will be captured in adverse effects of treatment.
Innovation	Vifor Fresenius Medical Care Renal Pharma UK	Yes. Clinical evidence exists to support the health-related benefits (morbidity and mortality) of using RAASi at the highest tolerated targeted doses that are recommended by guidelines in patients with CKD and CHF. Hyperkalaemia is a recognised side-effect of RAASi use which can lead to either reduction in doses or discontinuation of RAASi with the potential loss of the benefits on clinical outcomes. The addition of patiromer therefore represents a potential	Comment noted. The appraisal committee will consider the innovative nature of patiromer during the course of the appraisal.

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		significant and substantial health-related improvement to patients who would otherwise not be able to benefit from the continuous use of RAASi therapies. No. 1. Bakris GL, Pitt B, Weir MR, Freeman MW, Mayo MR, Garza D, et al. Effect of Patiromer on Serum Potassium Level in Patients With Hyperkalaemia and Diabetic Kidney Disease: The AMETHYST-DN Randomized Clinical Trial. JAMA. 2015;314(2):151-61. 2. Weir MR, Bakris GL, Bushinsky DA, Mayo MR, Garza D, Stasiv Y, et al. Patiromer in patients with kidney disease and hyperkalaemia receiving RAAS inhibitors. N Engl J Med. 2015;372(3):211-21. 3. Pitt B, Bakris GL, Bushinsky DA, Garza D, Mayo MR, Stasiv Y, et al. Effect of patiromer on reducing serum potassium and preventing recurrent hyperkalaemia in patients with heart failure and chronic kidney disease on RAAS inhibitors. European journal of heart failure. 2015;17(10):1057-65. 4. Buysse JM, Huang IZ, Pitt B. PEARL-HF: prevention of hyperkalaemia in patients with heart failure using a novel polymeric potassium binder, RLY5016. Future Cardiol. 2012;8(1):17-28.	
	AstraZeneca UK	There have been no drug launches for hyperkalaemia for over 50 years. Both sodium zirconium cyclosilicate (formerly ZS-9) and patiromer therefore offer a step change in the short- and long- term management of hyperkalaemia. Sodium zirconium cyclosilicate, specifically, is innovative in being an insoluble, non-absorbed, inorganic, zirconium silicate compound which acts as a highly selective potassium-removing agent, with rapid onset of action, efficacy up to one year, and stability at room temperature.	Comment noted. The appraisal committee will consider the innovative nature of patiromer during the course of the appraisal.

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	Kidney Care UK	This is likely to be a relatively small group of people who develop hyperkalaemia and having another treatment is welcome. Current treatment options are considered to be very unpleasant by patients. It should not remove the onus from clinicians, dieticians and other members of the healthcare team from working with patients (and families if appropriate) on any amenable causes of hyperkalaemia.	Comment noted. The appraisal committee will consider the innovative nature of patiromer during the course of the appraisal.
	Renal Association (endorsed by Royal College of Physicians)	The potential for this drug to impact HRQOL are significant but may not be easily measureable. The ability to relax diet from a patient perspective is a potential gain, leading to a healthier diet and less malnutrition in patients with CKD, dialysis and diabetes. This has a impact in the home in relation to the simply ability of cooking meals for the whole family and not segregating food. Data is not currently available. This is a new field of therapy with current limited options available. This therefore has the potential to expand the armoury to the clinician to treat hyperkalaemia and reduce unnecessary hospital admissions. The current data set is a mix of retrospective observational studies on the significant of hyperkalaemia in outcomes and therefore hypothesis generating while the recent randomised studies involving the drug in question against a comparator have biochemical endpoints to consider. No current hard end point data that I am aware of is currently available. There are a number of observational studies which I have detailed below which are worth considering.	Comment noted. The appraisal committee will consider the innovative nature of patiromer during the course of the appraisal.
Questions for consultation	Vifor Fresenius Medical Care Renal Pharma UK	a) Where do you consider patiromer will fit into the existing NICE pathways on acute kidney injury, chronic kidney disease and hypertension? Acute Kidney Injury (CG169)– patiromer should be used for pharmacological management before one refers for renal replacement therapy.	Comments noted.

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		Chronic kidney Disease (CG182)– Section1.6 Pharmacotherapy – patiromer can facilitate BP control by reducing potassium and consequently lowering aldosterone as an adjunct to antihypertensive agents (e.g. RAASi). Hypertension (CG 127)– patiromer can be used as an adjunct to Step 4 Treatment to help maintain potassium levels which will facilitate use of spironolactone as described in the guideline to control BP by reducing potassium and consequently lowering aldosterone. Heart Failure Guidelines (CG108) – Section 1.2.2 Pharmacological treatment of heart failure - For those whose treatment with ACE/ARBs are limited by the presence of hyperkalaemia, patiromer can facilitate continued treatment as necessary. b) To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly. Vifor does not consider that there are any barriers to the adoption of this technology. c) NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. Vifor would welcome a STA in this instance as we believe there is an urgent unmet need that patiromer will address. d) NICE has published an addendum to its guide to the methods of technology appraisal (available at https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/methods-guide-addendum-cost-comparison.pdf), which states the methods to be used where a cost comparison case is made. We welcome comments on the appropriateness and suitability of the cost comparison methodology to this topic.	

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		Vifor does not believe a direct cost-comparison is appropriate as there is currently no standard of care comparator. e) Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators? Patiromer is a first in class innovation. There is currently no appropriate comparator. f) Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant? Yes, it is still clinically relevant. g) Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year? There is no licenced comparator technology. However there is a technology in development for which trials are ongoing. See ClinicalTrial.gov for sodium zirconium cyclosilicate. h) In your response to the question about the relevant comparators, please could you let us know if sodium zirconium cyclosilicate should be included as a comparator? We do not consider sodium zirconium cyclosilicate as a comparator as it is not presently licensed and we are not aware of the timelines for such a review. However currently available data would suggest that sodium zirconium cyclosilicate would be most likely to be considered for the acute/emergency treatment of hyperkalaemia. i) Would there be value in adding sodium zirconium cyclosilicate as an intervention in addition to sodium patiromer in order to appraise these	

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		technologies through the Multiple Technology Appraisal (MTA) Process. Information on the NICE's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction)? No. Please be advised that patiromer is a calcium ion exchange polymer that doesn't contain sodium unlike sodium zirconium cyclosilicate. Patiromer exchanges potassium ions in the GI tract for calcium ions. This technology was specifically designed to avoid the potential well-known consequences/issues associated with extra sodium loads (e.g. hypertension, CHF, renal damage or oedema). At present we are aware that a marketing authorisation is being sought for sodium zirconium cyclosilicate. We are unable to comment on the timing, proposed indication nor potential outcome of their application. In light of the unmet clinical need that currently exists, and the uncertainty of the timelines for the availability of sodium zirconium cyclosilicate, we feel waiting for a MTA would be a disservice to patients who could benefit from patiromer now.	
	AstraZeneca UK	• In your response to the question about the relevant comparators, please could you let us know if sodium zirconium cyclosilicate should be included as a comparator? Following feedback from clinicians, sodium zirconium cyclosilicate and patiromer are expected to be used in a very similar setting in clinical practice. Due to a faster onset of action (medium time to normokalaemia = 2.2 hours) sodium zirconium cyclosilicate is additionally expected to be used to a greater extent than patiromer during the initiation phase of hyperkalaemia treatment. Therefore it would be appropriate to consider these products as relevant clinical comparators; [redacted]	Comments noted.

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		• Would there be value in adding sodium zirconium cyclosilicate as an intervention in addition to sodium patiromer in order to appraise these technologies through the Multiple Technology Appraisal (MTA) Process. Information on the NICE's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction)? [redacted]	
	Royal College of Pathologists	Additional questions: sodium zirconium cyclosilicate would be an additional useful comparator. This could be compared using MTA.	Comment noted.
	Renal Association (endorsed by Royal College of Physicians)	All comparators have been included but there is little comparative data and no head to head with resonium that I am aware of. Newer products are also in development. As detailed I would include the group >6.0 mmol/L. Again as detailed above. Patiromer based on the current literature would certainly fit with CKD and possibly with AKI and hypertension. Head to head data is less clear for the latter indications. The proposed remit and scope although not comprehensive at this juncture does cover important patient groups. However if limited to the current cohorts considered it may negate it use in potential other groups in the future where is some evidence but as jet not substantive, therefore a common sense approach should be adopted and a wider remit of allowance if deemed cost effective. (see details of references added). This is a step forward in an area of electrolyte control and to some extent in part may lead to a set change in management of heart failure for example with optimisation of ACEi/ARB use.	Comment noted.

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		Barriers to adoption are few and may relate to tolerability and side-affects. In addition data on mortality is observational and currently all end points are based on changes in serum potassium and no hard end points such as death, cardiovascular events or cerebrovascular events. Cost methodology is out with my expertise. There are a number of areas of research that should be considered - investigation of use in dialysis patients - longer term studies on maintaining K - head to head with resonium - transplant patients - elderly patients Implementation, including the resource availability to support implementation should not be an issue and I would expect that clinical practice would not be impacted, indeed it may possibly allow reduced monitoring, and assuming there is no significant increase in adverse effects. The timing of the appraisal review, may be premature with other molecules in the same field under study but this should not prevent assessment. The cost analysis for this current application maybe difficult as there is no one single comparator but a combination of interventions to reduce potassium. It may also be that this is additive therapy to optimise therapy so it is no clear how this cost analysis will be easily carried out.	
Additional comments on the draft scope	Vifor Fresenius Medical Care Renal Pharma UK	n/a	Response noted.
	Renal Association (endorsed by	Observational studies suggest benefit of reducing K post MI – one retrospective trial of 38,689 hospitalized patients with AMI treated in the modern era demonstrated an independent increase in mortality among patients with potassium levels .5.1 mmol/L (OR, 3.27; 95% CI, 2.52 to 4.24)	Comment noted.

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	Royal College of Physicians)	which persisted in patients with serum potassium levels of 4.5–5.0 mmol/L (OR, 1.99; 95% CI, 1.68 to 2.36). A subsequent analysis of this same cohort showed elevated in-hospital mortality with exposure to a higher number of hyperkalaemic episodes (13.4%, 16.2%, and 19.8% increase in mortality with one, two, and three or more potassium measurements .5.0 mmol/L, respectively) and maximum achieved serum potassium level (4.2%, 11.1%, 16.6%, 26.6%, and 31.7% increase in mortality with potassium levels ,5.0, 5.0–5.5, 5.5–6.0, 6.0–6.5, and .6.5 mmol/L, respectively). Goyal A, Spertus JA, Gosch K, Venkitachalam L, Jones PG, Van den Berghe G, KosiborodM: Serum potassium levels andmortality in acute myocardial infarction. JAMA 307: 157–164, 2012 Grodzinsky A, Goyal A, Gosch K, McCullough PA, Fonarow GC, Mebazaa A, Masoudi FA, Spertus JA, Palmer BF, Kosiborod M: Prevalence and prognosis of hyperkalemia in patients with acute myocardial Infarction. Am J Med 129: 858–865, 2016 A recently published retrospective observational trial of 52,734 patients on a X3/week haemodialysis schedule showed that potassium levels 5.5–6.0 mmol/L were associated with higher risk for subsequent hospitalization, emergency department visits, and mortality within 4 days of measurement. The association between hyperkalemia and hospitalization was magnified among patients entering a longer intradialytic interval (adjusted OR for hospitalization, 1.12; 95% CI, 1.0 to 1.24; OR, 1.04; 95% CI, 0.94 to 1.16; and OR, 1.68; 95% CI, 1.22 to 2.30 for patients with potassium measurements performed on Monday, Wednesday, and Friday, respectively). Brunelli SM, Du Mond C, Oestreicher N, Rakov V, SpiegelDM: Serum potassium and short-term clinical outcomes among hemodialysis patients: Impact of the long interdialytic interval. Am J Kidney Dis 70: 21–29, 2017	

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		Nakhoul GN, Huang H, Arrigain S, Jolly SE, Schold JD, Nally JV Jr., Navaneethan SD: Serum potassium, end-stage renal disease and mortality in chronic kidney disease. Am J Nephrol 41: 456–463, 2015 Newer agents, such as sodium zirconium cyclosilicate (ZS-9; AstraZeneca) and patiromer (Veltassa; Relypsa), have been demonstrated to effectively lower serum potassium when administered in patients with chronic hyperkalemia at levels <6.5 mmol/L. Interestingly potassium may be rapidly lowered within hours by both ZS-979 and patiromer suggesting a previously unrecognized role of the upperGI tract in potassium regulation. Weir MR, Bakris GL, Bushinsky DA, Mayo MR, Garza D, Stasiv Y, Wittes J, Christ- Schmidt H, Berman L, Pitt B; OPAL-HK Investigators: Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. N Engl J Med 372: 211–221, 2015 Bakris GL, Pitt B, Weir MR, Freeman MW, Mayo MR, Garza D, Stasiv Y, Zawadzki R, Berman L, Bushinsky DA; AMETHYST-DN. Investigators: Effect of patiromer on serum potassium level in patients with hyperkalemia and diabetic kidney disease: The AMETHYST-DN randomized clinical trial. JAMA 314: 151–161, 2015 Packham DK, Rasmussen HS, Lavin PT, El- ShahawyMA, Roger SD, Block G, Qunibi W, Pergola P, Singh B: Sodium zirconium cyclosilicate in hyperkalemia. N Engl J Med 372: 222–231, 2015 Kosiborod M, Rasmussen HS, Lavin P, Qunibi WY, Spinowitz B, Packham D, Roger SD, Yang A, Lerma E, Singh B: Effect of sodium zirconium cyclosilicate on potassium lowering for 28 days among outpatients with hyperkalemia: The HARMONIZE randomized clinical trial. JAMA 312: 2223–2233, 2014 Bushinsky DA,WilliamsGH, Pitt B,WeirMR, Freeman MW, Garza D, Stasiv Y, Li E, Berman L, Bakris GL: Patiromer induces rapid and sustained potassium lowering in patients with chronic kidney disease and hyperkalemia. Kidney Int 88: 1427–1433, 2015	

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

British Society for Heart Failure
Department of Health
Kidney Research UK
Pumping Marvellous Foundation