New Medicine Recommendation

Patiromer sorbitex calcium (Veltassa) powder for oral suspension

For the treatment of hyperkalaemia in adults.

Proposed use: As a once daily alternative to Calcium Resonium for the treatment of hyperkalaemia in adults.

Recommendation: Red

Patiromer is recommended as a once daily alternative to Calcium Resonium for the treatment of hyperkalaemia in adults. The following conditions apply:

- Medicine is supplied by the hospital for the duration of the treatment course.
- Primary care initiation or continuation of treatment is not recommended unless exceptional circumstances such as specialist GP.

Red medicines are those where primary care prescribing is not recommended. These treatments should be initiated by specialists only and prescribing retained within secondary care. They require specialist knowledge, intensive monitoring, specific dose adjustments or further evaluation in use. If however, a primary care prescriber has particular specialist knowledge or experience of prescribing a particular drug for a particular patient it would not always be appropriate for them to expect to transfer that prescribing responsibility back to secondary care. There should be a specific reason and a specific risk agreement, protocol and service set up to support this.

Primary care prescribers may prescribe RED medicines in exceptional circumstances to patients to ensure continuity of supply while arrangements are made to obtain on going supplies from secondary care.

Summary of supporting evidence

The safety and efficacy of Veltassa were demonstrated in a two-part, single blind randomised withdrawal study (RLY5016-301)[1] that evaluated the treatment in hyperkalaemic patients with chronic kidney disease (CKD) on stable doses of at least one RAAS inhibitor (i.e. angiotensin converting enzyme inhibitor [ACEI], angiotensin II receptor blocker [ARB] or aldosterone antagonist [AA]).

In Part A, 243 patients were treated with Veltassa for 4 weeks. Patients with a baseline serum potassium of 5.1 mEq/L to <5.5 mEq/L (mmol/L) received a starting dose of 8.4 g patiromer per day (as a divided dose) and patients with a baseline serum potassium of 5.5 mEq/L to <6.5 mEq/L received a starting dose of 16.8 g patiromer per day (as a divided dose). The dose was titrated, as needed, based on the serum potassium level, assessed starting on Day 3 and then at weekly visits to the end of the 4 week treatment period, with the aim of maintaining serum potassium in the target range (3.8 mEq/L to <5.1 mEq/L). The mean daily doses of Veltassa were 13 g and 21 g in patients with serum potassium of 5.1 to <5.5 mEq/L and 5.5 to <6.5 mEq/L, respectively.

The mean age of patients was 64 years (54% aged 65 and over, 17% aged 75 and over), 58% of patients were men, and 98% were Caucasian. Approximately 97% of patients had hypertension, 57% had type 2 diabetes, and 42% had heart failure.

Mean serum potassium levels and change in serum potassium from Part A Baseline to Part A Week 4 is shown in Table 1. For the Part A secondary outcome, 76% (95% CI: 70%, 81%) of patients had a serum potassium in the target range of 3.8 mEq/L to <5.1 mEq/L at Part A Week 4.

Veltassa Treatment Phase (Part A): Primary Endpoint

	Baseline Potassium		Overall Population (n=237)
	5.1 to <5.5 mEq/L (n=90)	5.5 to <6.5 mEq/L (n=147)	
	Serum Potassium (mEq/L)		
Baseline, mean (SD)	5.31 (0.57)	5.74 (0.40)	5.58 (0.51)
Week 4 Change from Baseline, Mean ± SE (95% CI)	−0.65 ± 0.05 (−0.74, −0.55)	−1.23 ± 0.04 (−1.31, −1.16)	−1.01 ± 0.03 (−1.07, −0.95)
p value			<0.001

In Part B, 107 patients with a Part A baseline serum potassium of 5.5 mEq/L to <6.5 mEq/L and whose serum potassium was in the target range (3.8 mEq/L to <5.1 mEq/L) at Part A Week 4 and still receiving RAAS inhibitor treatment were randomised to continue Veltassa or to receive placebo for 8 weeks to evaluate the effect of withdrawing Veltassa on serum potassium.

In patients randomised to Veltassa, the mean daily dose was 21g at the start of Part B and during Part B.

The Part B primary endpoint was the change in serum potassium from Part B baseline to the earliest visit at which the patient's serum potassium was first outside of the range of 3.8 to <5.5 mEq/L or to Part B Week 4 if the patient's serum potassium remained in the range. In Part B, serum potassium in patients on placebo increased significantly relative to patients who remained on Veltassa (p<0.001).

More placebo patients (91% [95% CI: 83%, 99%]) developed a serum potassium ≥5.1 mEq/L at any time during Part B than Veltassa patients (43% [95% CI: 30%, 56%]), p<0.001. More placebo patients (60% [95% CI: 47%, 74%]) developed a serum potassium ≥5.5 mEq/L at any time during Part B than Veltassa patients (15% [95% CI: 6%, 24%]), p<0.001.

The potential of Veltassa to enable concomitant RAAS inhibitor treatment was also assessed in part B. Fifty two percent (52%) of subjects receiving placebo discontinued RAAS inhibitor treatment because of recurrent hyperkalaemia compared with 5% of subjects treated with Veltassa.

The effect of treatment with Veltassa for up to 52 weeks was evaluated in an open label study of 304 hyperkalaemic patients with CKD and type 2 diabetes mellitus on stable doses of a RAAS inhibitor (RLY5016-205)[2]. The mean age of patients was 66 years (59.9% aged 65 and over, 19.7% aged 75 and over), 63% of patients were men, and all were Caucasian. Decreases in serum potassium with Veltassa treatment were maintained over 1 year of chronic treatment, with a low incidence of hypokalaemia (2.3%) and the majority of subjects reaching (97.7%) and maintaining target serum potassium levels (overall during maintenance period, serum potassium was within the target range for approximately 80% of the time). In patients with a baseline serum potassium of >5.0 to 5.5 mEq/L who received an initial dose of 8.4 g patiromer per day, the mean daily dose was 14 g; in those with a baseline serum potassium of >5.5 to <6.0 mEq/L who received an initial dose of 16.8 g patiromer per day, the mean daily dose was 20 g during the entire study.

Details of Review

Name of medicine (generic & brand name):[3] Patiromer sorbitex calcium (Veltassa) powder for oral suspension.
Strengths and forms:

8.4 g or 16.8 g of patiromer, as powder in sachets. Pack sizes: boxes of 30 sachets.
Dose and administration: The recommended starting dose is 8.4 g patiromer 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 8.4 g as necessary to reach the desired target range, up to a maximum dose of 25.2 g daily. If serum potassium falls below the desired range, the dose should be reduced or discontinued. If a dose is missed, the missed dose should be taken as soon as possible on the same day. The missed dose should not be taken with the next dose. Administration of Veltassa should be separated by 3 hours from other oral medicinal products. The onset of action of Veltassa occurs 4 – 7 hours after administration. Veltassa should not replace emergency treatment for life threatening hyperkalaemia
BNF therapeutic class / mode of action: Chapter 9, Blood and nutrition, Nutrition and metabolic disorders Veltassa is a non -absorbed, cation exchange polymer that contains a calcium-sorbitol complex as a counterion and manufactured as free-flowing spherical beads of approximately 100 micrometer diameter which are taken orally. The beads are of a size that is not absorbed. It increases faecal potassium excretion through binding of potassium in the lumen of the gastrointestinal tract. Binding of potassium reduces the concentration of free potassium in the gastrointestinal lumen resulting in a reduction of serum potassium levels. Veltassa contains calcium as part of the counterion complex. Calcium is partially released some of which may be absorbed. The benefits and risks of administering this medicinal product should be carefully evaluated in patients at risk of hypercalcaemia. Veltassa contains sorbitol as part of the counterion complex. The sorbitol content is approximately 4 g (10.4 kcal) per 8.4 g of patiromer. Veltassa increases faecal potassium excretion through binding of potassium in the lumen of the gastrointestinal tract. Binding of potassium reduces the concentration of free potassium in the gastrointestinal lumen, resulting in a reduction of serum potassium levels
Licensed indication(s): Veltassa is indicated for the treatment of hyperkalaemia in adults
Proposed use: Within licensed indication.
Course and cost: Veltassa is supplied in boxes containing 30 sachets of either 8.4g or 16.8g of patiromer. The NHS cost for 1 box of 30 sachets of either strength is £300. The monthly cost may vary from £300 (8.4g / day, 16.8g / day) to £600 (at maximum daily dose of 25.2g)
Current standard of care/comparator therapies: Patients with severe acute hyperkalaemia, or with electrocardiogram (ECG) changes related to hyperkalaemia, are generally already hospitalized or sent to the hospital for treatment. The therapeutic goals in such hospitalized patients with severe hyperkalaemia are: temporarily stabilisation of the myocardium, temporarily shift in intracellular potassium and utilisation of treatments that remove potassium from the body, which are intended to reduce the risk for developing a fatal cardiac arrhythmic event. For patients in whom the aetiology of hyperkalaemia is not reversible but rather more chronic in nature from underlying CKD and/or use of renin angiotensin aldosterone system inhibitors (RAASi) therapies, the traditional approach to management has relied on dietary potassium restriction, RAASi dose reduction or

discontinuation, diuretics, oral bicarbonate and if applicable, the use of the cation exchange resins sodium polystyrene sulfonate or calcium polystyrene sulfonate. The use of dietary potassium restriction to manage hyperkalaemia is difficult due to the ubiquitous presence of potassium in foods.

Sodium polystyrene sulfonate and calcium polystyrene sulfonate are two cation-exchange resins currently approved in the UK for the treatment of hyperkalaemia. They were introduced in the 1950s and 1960s; however, have not been rigorously studied. 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. The usual oral dose is 15g three or four times a day, the resin may also be given rectally as a suspension of 30g resin in 150ml of water or 10% dextrose, as a daily retention enema.

Both calcium and sodium polystyrene sulfonate are contraindicated for treating patients with a serum potassium < 5.0 mEq/L and both require 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.

Relevant NICE guidance:

NICE – not reviewed

SMC – not reviewed

AWMSG – Excluded from review August 2017 - Product is a preparation for fluid and electrolyte imbalance

Disease Background

Elevation of the plasma potassium concentration decreases the ratio of intracellular to extracellular potassium, leading to partial depolarization of the cell membrane. These physiological effects of hyperkalaemia can result in muscle weakness, paralysis, life-threatening effects on cardiac conduction (e.g., QRS widening), arrhythmias such as ventricular fibrillation and sudden death. Thus, hyperkalaemia represents a serious condition that can result in life-threatening cardiac arrhythmias and is associated with increased mortality risk. While rare in the healthy individuals with normal renal function, the prevalence of hyperkalaemia in patients with renal insufficiency or chronic kidney disease (CKD) ranges from 5% to 50% and increases as renal function declines. Thus, patients most at risk of hyperkalaemia are those with compromised renal excretion of potassium, primarily patients with CKD and/or patients being treated with drugs that inhibit renal potassium excretion, including renin angiotensin aldosterone system inhibitors (RAASi). RAASi are used in the treatment of hypertension, CKD and congestive heart failure and compelling data and clinical practice guidelines support the use of RAASi to reduce adverse cardiovascular and renal outcomes in certain high-risk patient populations. However, therapy with RAASi can be limited by hyperkalaemia resulting from treatment with these medications. In addition to CKD and the use of RAASi, diabetes and the use of beta-blockers can increase the risk of hyperkalaemia leading to fatal cardiac arrhythmias.

Potassium balance is regulated in part by secretion of potassium into the colon through a passive paracellular route and active secretion. Hence in the colon, potassium is at high concentration relative to other cations. In CKD, urinary excretion of potassium decreases and colonic secretion of potassium increases substantially. Hyperkalaemia can present as a consequence of a number of acute clinical conditions that occur in a hospital setting. Based on literature data, approximately 14% of patients experienced a hyperkaliaemic event and the rate was higher in patients with CKD than in those without CKD. Acute clinical conditions such as tumour lysis syndrome, rhabdomyolysis, crush injuries, massive blood transfusions and acute renal failure can each lead to a rise in serum potassium to high levels. These acute clinical conditions require immediate treatment for the hyperkalaemia, particularly when the degree of

hyperkalaemia is severe (e.g. serum potassium ≥ 6.5 mEq/L) and/or associated with cardiac repolarization disturbances. The risk of death is increased significantly in CKD patients with hyperkalaemia, underscoring the need to treat this clinical condition.

Current treatment options

Sodium polystyrene sulfonate and calcium polystyrene sulfonate are two cation-exchange resins currently approved in the UK for the treatment of hyperkalaemia.

Sodium Polystyrene Sulfonate 99.934% w/w (Resonium A)[4] is an ion-exchange resin that is recommended for the treatment of hyperkalaemia associated with anuria or severe oliguria. It is also used to treat hyperkalaemia in patients requiring dialysis and in patients on regular haemodialysis or on prolonged peritoneal dialysis. The usual dose is 15g three or four times a day. Each dose should be given as a suspension in a small amount of water or, for greater palatability, in syrup (but not fruit juices which contain potassium), in the ratio of 3 to 4ml per gram of resin.

The rectal route should be reserved for the patient who is vomiting or who has upper gastrointestinal tract problems, including paralytic ileus or it may be used simultaneously with the oral route for more rapid initial results. The resin may be given rectally as a suspension of 30g resin in 150ml of water or 10% dextrose, as a daily retention enema. In the initial stages administration by this route as well as orally may help to achieve a more rapid lowering of the serum potassium level.

The enema should if possible be retained for at least nine hours following which the colon should be irrigated to remove the resin. If both routes are used initially it is probably unnecessary to continue rectal administration once the oral resin has reached the rectum.

Contraindications include:

- patients with plasma potassium levels below 5mmol/litre.
- History of hypersensitivity to polystyrene sulfonate resins.
- Obstructive bowel disease.
- Resonium A should not be administered orally to neonates and is contraindicated in neonates with reduced gut motility (post-operatively or drug-induced).

Gastrointestinal stenosis, intestinal ischemia and its complications (necrosis and perforation) may occur in patients treated with polystyrene sulfonate, especially in patients using sorbitol. Therefore, concomitant use of Sorbitol with sodium polystyrene sulfonate is not recommended.

The possibility of severe potassium depletion should be considered, and adequate clinical and biochemical control is essential during treatment, especially in patients on digitalis. Administration of the resin should be stopped when the serum potassium falls to 5mmol/litre.

Care should be taken when administering to patients in whom an increase in sodium load may be detrimental (i.e. congestive heart failure, hypertension, renal damage or oedema). In such instances, adequate clinical and biochemical control is essential. The calcium form of the resin may have advantages in this situation.

Calcium Resonium 99.934% w/w Powder for Oral/Rectal Suspension[5] is an ion-exchange resin that is recommended for the treatment of hyperkalaemia associated with anuria or severe oliguria. It is also used to treat hyperkalaemia in patients requiring dialysis and in patients on regular haemodialysis or on prolonged peritoneal dialysis. The usual dose is 15g three or four times a day. Each dose should be given as a suspension in a small amount of water or, for greater palatability, in syrup (but not fruit juices which contain potassium), in the ratio of 3 to 4ml per gram of resin. The rectal route should be reserved for the patient who is vomiting or who has upper gastrointestinal tract problems, including paralytic ileus or it may be used simultaneously with the oral route for more rapid initial results. The resin may be given rectally as a suspension of 30g resin in 150ml of water or 10% dextrose, as a daily retention enema. In the initial stages administration by this route as well as orally may help to achieve a rapid lowering of the serum potassium level.

The enema should if possible be retained for at least nine hours, then the colon should be irrigated to remove the resin. If both routes are used initially it is probably unnecessary to continue rectal administration once the oral resin has reached the rectum.

Contraindications include:

- Patients with plasma potassium levels below 5mmol/litre.
- Conditions associated with hypercalcaemia (e.g. hyperparathyroidism, multiple myeloma, sarcoidosis or metastatic carcinoma).
- History of hypersensitivity to polystyrene sulfonate resins.
- Obstructive bowel disease.
- Calcium Resonium should not be administered orally to neonates and is contraindicated in neonates with reduced gut motility (post-operatively or drug-induced).
- Hypersensitivity to the active substance or to any of the excipients.

Gastrointestinal stenosis, intestinal ischemia and its complications (necrosis and perforation) may occur in patients treated with polystyrene sulfonate, especially in patients using sorbitol. Therefore, concomitant use of Sorbitol with calcium polystyrene sulfonate is not recommended.

The possibility of severe potassium depletion should be considered and adequate clinical and biochemical control is essential during treatment, especially in patients on digitalis. Administration of the resin should be stopped when the serum potassium falls to 5mmol/litre.

Like all cation-exchange resins, calcium polystyrene sulfonate is not totally selective for potassium. Hypomagnesaemia and/or hypercalcaemia may occur. Accordingly, patients should be monitored for all applicable electrolyte disturbances. Serum calcium levels should be estimated at weekly intervals to detect the early development of hypercalcaemia, and the dose of resin adjusted to levels at which hypercalcaemia and hypokalaemia are prevented.

The NHS cost of **Sodium Polystyrene Sulfonate 99.934% w/w (Resonium A)** is £81.11for 454g. [6]

- For a patient on a dose of 15g three times daily this equates to 1,350g for 30 days treatment = 3 x 454g tubs at a cost of £243.33.
- For a patient on a dose of 15g four times daily this equates to 1,800 g for 30 days treatment = 4 x 454g tubs at a cost of £324.44

The NHS cost of **Calcium Resonium 99.934% w/w Powder for Oral/Rectal Suspension** is £82.16 for 300g.[6]

- For a patient on a dose of 15g three times daily this equates to 1,350g for 30 days treatment =4.5 x 300g tubs , if 5 tubs provided = £410.80
- For a patient on a dose of 15g four times daily this equates to 1,800 g for 30 days treatment = 6 x 300g tubs at a cost of £492.96.

Over the last twelve months across Lancashire **within Primary Care** there has been no prescribing of Sodium Polystyrene Sulfonate 99.934% w/w (Resonium A) and the total expenditure for Calcium Resonium 99.934% w/w Powder for Oral/Rectal Suspension was £14,891.50 = approx. 180 x 300g tubs.

Summary of efficacy data in proposed use:

The clinical programme for patiromer comprises twenty studies: three Phase 1 clinical pharmacology studies, twelve single dose drug-drug interaction studies, four Phase 2 studies and one two-part Phase 3 study. In clinical studies in patients with chronic kidney disease (CKD), heart failure (HF) or on haemodialysis, the duration of administration of study drug ranged from 48 hours to 52 weeks and the doses ranged from 8.4 to 50.4 g/day patiromer. The dosing regimen for the marketed product is once daily up to a maximum dose of 25.2 g/day.

Of the Phase 2 /3 studies, Studies 301 and 205 are considered “Treatment Studies” because subjects enrolled in these studies had elevated serum potassium at baseline.

Study RLY5016-205 [2]: Multicentre, Randomised, Open, Dose Ranging Study to Evaluate the Efficacy and Safety of patiromer in the treatment of Hyperkalaemia in Patients with Hypertension and Diabetic Nephropathy Receiving ACEI and/or ARB Drugs, with or without Spironolactone. (Phase 2). The primary objective of the study was to determine the optimal starting dose of patiromer in treating hyperkalaemia in subjects with hypertension and diabetic nephropathy receiving angiotensin-converting enzyme inhibitor (ACEI) and/or angiotensin II receptor blocker (ARB) drugs, with or without spironolactone. Secondary objectives were to determine the safety and efficacy of patiromer in treating hyperkalaemia in the above population and to evaluate the chronic use of patiromer. The study had two treatment periods; firstly a treatment initiation period (TIP) lasting 8 weeks, followed by a Long-term Maintenance Period for an additional 44 weeks. Eligible subjects with screening serum potassium of 4.3 to 5.0 mEq/L and uncontrolled hypertension started a Run-in Period of 1 to up to 4 weeks in duration. During which Cohort 1 subjects discontinued pre-study RAASi medication and started losartan 100 mg. Spironolactone was added if necessary for additional blood pressure control. Cohort 2 subjects continued on their pre-study ACEI or ARB medication and added spironolactone to the regimen. Cohort 3 had serum potassium > 5.0 to < 6.0 mEq/L at screening or start of the Run-in Period and entered the TIP immediately while continuing to receive their current ACEI and/or ARB regimen. Subjects from all three cohorts were assigned to one of two strata according to baseline serum potassium:

- Stratum 1 (serum potassium values > 5.0 to 5.5 mEq/L) subjects were randomised to one of three patiromer starting doses: 8.4, 16.8, or 25.2 g/day patiromer
- Stratum 2 (serum potassium values > 5.5 to < 6.0 mEq/L) subjects were randomised to one of three patiromer starting doses: 16.8, 25.2, or 33.6 g/day patiromer

All patiromer doses were administered **BID**. Doses of patiromer were titrated based on individual subject response to achieve and maintain serum potassium in the range of 4.0 to 5.0 mEq/L during the 8-week TIP and in the range of 3.8 to 5.0 mEq/L during the 44 week LTMP. The dose of patiromer could be adjusted starting on Day 3 and up to the Week 51 Visit according to a titration algorithm that was designed to maintain serum potassium levels within a target range. An interim data analysis was performed based on data collected from approximately 20 subjects per starting dose group who completed the Week 4 treatment visit or who had prematurely discontinued from the study and had primary efficacy data. The mean change in central laboratory serum potassium from baseline to Week 4 (or prior to the initiation of patiromer dose titration, if occurs before Week 4) and its standard deviation (SD) for each starting dose group were calculated based on this interim data set. These interim results were used to determine the optimal starting dose of patiromer for each serum potassium stratum for future studies.

The primary efficacy endpoint was the mean change in serum potassium from baseline to Week 4 (or prior to titration of the patiromer dose, if it occurred prior to Week 4).

Results

306 subjects were randomised of whom 304 received study treatment. A total of 266 subjects completed the 8-week TIP and 197 completed the one year study period. A majority of the 304 subjects were male (63%) and all were Caucasian with a mean (±SD) age of 66.3 ± 8.61 years (range 37 to 80). In both strata, the highest percentages of subjects had screening CKD stages of Stage 3a, 3b, or 4 (based on screening eGFR results). Subjects in the Stratum 2 starting dose groups with higher mean serum potassium levels at baseline had lower mean eGFR at study entry, and there were higher proportions of subjects with CKD Stage 4 or 5 in Stratum 2 compared with Stratum 1. All subjects had T2DM and hypertension.

The mean change from baseline in serum potassium at Week 4 or prior to dose titration was statistically significant for all dose groups within both strata ($p < 0.001$). The observed least square (LS) mean (SE) overall change at Week 4 in Stratum 1 was - 0.47 (0.039) mEq/L. The LS mean (SE) overall change in Stratum 2 was - 0.92 (0.075) mEq/L.

Treatment Initiation Period: Mean decreases in serum potassium from baseline to all time points during the TIP (regardless of titration) were observed for each starting dose group within both strata, including at Day 3 following administration of approximately 4 doses of patiromer. Throughout the entire TIP, the LS mean change from baseline in Stratum 2 were consistently larger than those in Stratum 1. The range of the LS mean (SE) change from baseline overall for Stratum 2 was -0.59 (0.048) mEq/L (Day 3) to -1.14 (0.051) mEq/L (Week 5) and for Stratum 1 was -0.29 (0.028) mEq/L (Day 3) to -0.66 (0.027) mEq/L (Week 5). At Week 4, the proportion of Stratum 1 subjects with serum potassium within the range of 4.0 to 5.0 mEq/L was 85.4% and for Stratum 2 was 72.6%, and at 8 weeks was 89.1% and 82.9%, respectively.

Long-Term Maintenance Period: Regardless of stratum or starting dose, mean serum potassium values were decreased from baseline at every time point during the LTMP. The mean change from baseline in serum potassium for Stratum 1 subjects at all LTMP time points was approximately -0.50 mEq/L, and the mean change from baseline for Stratum 2 subjects for the same time points was approximately -1.00 mEq/L. At Week 28, the proportion of Stratum 1 subjects with serum potassium within the range of 3.8 to 5.0 mEq/L was 89.0% and for Stratum 2 was 95.1%, and at 52 weeks was 85.5% and 89.8%, respectively.

Post-treatment Follow-up: Serum potassium values started to increase after treatment with patiromer was discontinued. At Days 3 and 7 of the Follow-up Period the mean (SD) change from the end of treatment was 0.22 (0.453) mEq/L (n = 163) and 0.29 (0.503) mEq/L (n = 154), respectively, for subjects in Stratum 1 and 0.29 (0.564) mEq/L (N = 58) and 0.46 (0.540) mEq/L (n = 57), respectively, for subjects in Stratum 2.

Based on a pre-planned interim analysis, the lowest effective dose in each stratum was selected as starting doses for Phase 3 in the absence of a clear dose-dependent response. For subjects with baseline serum potassium of 5.1 to < 5.5 mEq/L, the selected starting dose was 8.4 g/day patiromer, and for subjects with a baseline serum potassium of ≥ 5.5 to < 6.5 mEq/L the selected starting dose was 16.8 g/day patiromer.

Pivotal trial RLY5016-301[1]

A two part, single-blind, phase 3 study evaluating the efficacy and safety of patiromer for the treatment of hyperkalaemia.

This was a single-blind study in patients with chronic kidney disease (CKD) with estimated glomerular filtration rate (eGFR) at least 15 mL/min/1.73m^2 and less than 60 mL/min/1.73 m^2 who were receiving a stable dose of at least one renin angiotensin aldosterone system inhibitor (RAASi). At the beginning of the study, subjects were required to be hyperkalaemic with serum potassium of 5.1 to < 6.5 mEq/L. The study consisted of two sequential parts: Part A was an assessment of 4 weeks of dosing with patiromer in the treatment of hyperkalaemia; Part B was a randomised, placebo-controlled, 8-week assessment of the withdrawal of patiromer conducted in those subjects with a baseline serum potassium at the beginning of Part A ≥ 5.5 mEq/L who responded to the 4 weeks of treatment with patiromer.

Subjects who met eligibility criteria were assigned to one of two starting dose groups:

- Group 1 – Subjects with a Part A screening serum potassium of 5.1 to < 5.5 mEq/L were assigned to a starting dose of 8.4 g/day patiromer (4.2 g twice daily).
- Group 2 – Subjects with a Part A screening serum potassium of 5.5 to < 6.5 mEq/L were assigned to a starting dose of 16.8 g/day patiromer (8.4 g twice daily).

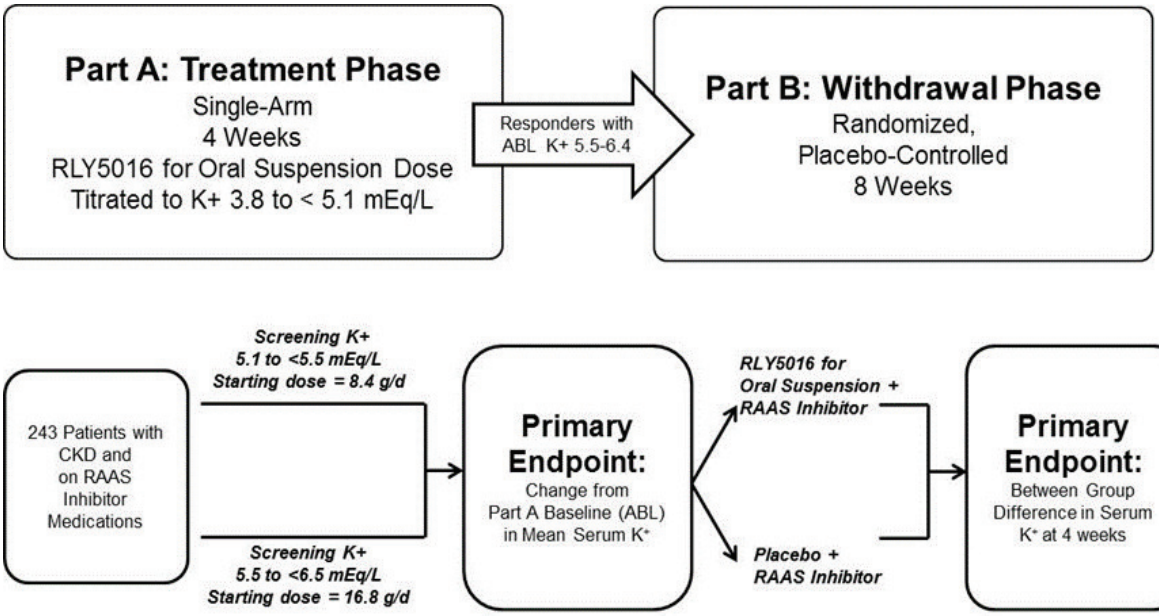
To be eligible for Part B, subjects had to meet all of the following; baseline serum potassium at the beginning of Part A ≥ 5.5 mEq/L, completed the four weeks of dosing with patiromer in Part A, serum potassium at the Part A Week 4 visit in target range for Part A (≥ 3.8 mEq/L and < 5.1 mEq/L), receiving patiromer at a dose of 8.4 to 50.4 g/day at the Part A Week 4 visit, and still receiving treatment with a RAASi at the Part A Week 4 visit.

During Part A, the patiromer dose was titrated, if needed, based on the serum potassium level starting at Day 3 and continuing to the end of 4 weeks with the aim of achieving serum

potassium in a target range of 3.8 to < 5.1 mEq/L. If a subject's serum potassium level was outside of the target range, patiromer dose titration was performed according to a protocol. The patiromer dose could be titrated to a maximum of 50.4 g/day; in increments of ±8.4 g/day. If the serum potassium level was ≥ 6.5 mEq/L or if the serum potassium level was ≥ 5.1 mEq/L and the subject was receiving the maximum dose of patiromer the RAASi was to be stopped. Subjects who withdrew from the study during the 4 weeks of Part A or who, at the end of Part A, were not eligible for Part B, entered a 1 to 2-week follow-up period to Part A.

Part B was a randomised, placebo-controlled, 8-week assessment of the withdrawal of patiromer. Subjects with a baseline serum potassium ≥ 5.5 mEq/L at the beginning of Part A were entered into Part B if they had responded to the 4 weeks of treatment with patiromer defined as completing Part A and satisfying all of the following at Week 4 visit; serum potassium in the range 3.8 to < 5.1 mEq/L, receiving a RAASi and receiving patiromer at a dose of 8.4 to 50.4 g/day. Subjects eligible for Part B were randomised 1:1 to either continue patiromer at the same daily dose or withdraw patiromer and receive placebo for an additional 8 weeks.

During Part B, patiromer (and RAASi) dose modification or discontinuation was performed according to protocol-specified titration algorithms based on serum potassium levels assessed starting at the Part B Day 3 visit and continuing through weekly visits to the end of the 8 week withdrawal phase. Because the primary efficacy endpoint for Part B was determined during the first 4 weeks of Part B, the titration algorithm specified no change of dose or discontinuation of patiromer or RAASi during the first 4 weeks of Part B unless the serum potassium level was < 3.8 mEq/L or ≥ 5.5 mEq/L. If a subject's serum potassium was < 3.8 mEq/L, the subject was withdrawn. To help retain subjects in the study an intervention (increase in patiromer or, for subjects receiving placebo, decrease in RAASi dose) was specified during the first 4 weeks of Part B. If a subject's serum potassium was ≥ 5.5 mEq/L after the first 4 weeks of Part B, the titration algorithm also specified an increase in patiromer dose upon the initial occurrence of a serum potassium ≥ 5.1 mEq/L. During Part B, the patiromer dose could be increased to a maximum of 50.4 g/day in increments of 8.4 g/day.



Objectives were:

Part A: To evaluate the efficacy and safety of patiromer for the treatment of hyperkalaemia.
Part B:

- To evaluate the effect of withdrawing patiromer on serum potassium control;

- To assess whether chronic treatment with patiromer prevents the recurrence of hyperkalaemia
- To provide placebo-controlled safety data.

A total of 243 subjects were enrolled in Part A; 92 (38%) had a screening serum potassium of 5.1 to < 5.5 mEq/L and were assigned to Dose Group 1 (starting dose of 8.4 g/day patiromer; 151 (62%) had a screening serum potassium of 5.5 to < 6.5 mEq/L and were assigned to Dose Group 2 (starting dose of 16.8 g/day patiromer). A total of 219 subjects; 92% of Group 1 and 89% of Group 2 completed the 4 weeks of Part A and 24 subjects 8% of Group 1 and 11% of Dose Group 2 withdrew early.

Of the 243 subjects enrolled in Part A, 121 (50%) either did not complete Part A or did not have a Part A baseline serum potassium ≥ 5.5mEq/L and were therefore not eligible for Part B. Of the remaining 122 subjects, 110 (90%) met the criteria for having responded to patiromer during Part A. Three of the 110 elected not to participate in Part B; 107 subjects were randomised in Part B 52 to placebo and 55 to continue patiromer. Of the 107 subjects in the Part B ITT population, 70% overall; 58% of the placebo group and 82% of the patiromer group completed the 8 weeks of dosing in Part B; 32 subjects 30% overall; 42% of the placebo group and 18% of the patiromer group withdrew early from Part B.

Part A Results

The mean (standard error [SE]) change in serum potassium from Part A Baseline to Part A Week 4 was -1.01 (0.031) mEq/L (95% CI: [-1.07, -0.95]); this mean reduction in serum potassium was statistically significantly different ($p < 0.001$). The mean change from baseline in serum potassium at Week 4 in Dose Group 1 was -0.65 mEq/L (95% CI: [-0.74, -0.55]) and the mean change from baseline in serum potassium in Dose Group was -1.23 mEq/L (95% CI: [-1.31, -1.16]).

The proportion of subjects with a serum potassium level in the Part A target range of 3.8 to < 5.1 mEq/L at Week 4 was 76% (95% CI: [70%, 81%]). Similar percentages were observed in each starting dose group (Dose Group 1: 74%; Dose Group 2: 77%.
Examination of mean serum potassium over time during Part A showed an overall mean change from baseline in serum potassium of -0.45 mEq/L by the Day 3 visit. For subjects in starting Dose Group 1, mean serum potassium was brought into the range of 3.8 to < 5.1 mEq/L at Day 3, with mean serum potassium stabilizing within 2 weeks. For subjects in starting Dose Group 2, mean serum potassium was brought into the range of 3.8 to < 5.1 mEq/L by Week 1, with the mean serum potassium stabilizing by Week 3.

Part B Results

The estimated difference in median change from Part B baseline (placebo minus patiromer powder for oral suspension) was 0.72 mEq/L with 95% CI (0.46, 0.99); $p < 0.001$ for between-group difference in mean ranks of change. The estimated median change from Part B baseline in serum potassium in the placebo group was an increase of 0.72 mEq/L while the estimated median change from baseline in serum potassium in the patiromer powder for oral suspension group was 0.00 mEq/L. A significant result on the primary endpoint provides evidence that treatment with patiromer is beneficial in maintain serum plasma levels in responding patients. However, because of the design (with measurements not available after serum potassium goes outside the range 3.8 to < 5.5 mEq/L) the estimates of the size of the benefit are not considered fully reliable and should be treated with caution.

Secondary Endpoints:

- Serum potassium ≥ 5.5 mEq/L at any time: The estimated proportion of subjects with a serum potassium ≥ 5.5 mEq/L at any time during the 8 weeks of Part B was 60% in the placebo group (95% CI of [47%, 74%]) and 15% in the patiromer powder for oral suspension group (95% CI of [6%, 24%]); the estimated difference in percentages (placebo minus patiromer powder for oral suspension) was 45% (95% CI of [29%, 61%]) and was statistically significant ($p < 0.001$).

- Serum potassium ≥ 5.1 mEq/L at any time: As noted above, subjects were eligible for Part B if the Part A Baseline serum potassium was ≥ 5.5 mEq/L. The estimated proportion of subjects with a serum potassium ≥ 5.1 mEq/L at any time during the 8 weeks of Part B was 91% in the placebo group (95% CI of [83%, 99%]) and 43% in the patiromer powder for oral suspension group (95% CI of [30%, 56%]); the estimated difference in percentages (placebo minus patiromer powder for oral suspension) was 48% (95% CI of [33%, 63%]) and was statistically significant ($p < 0.001$).

It is important to note that the study was almost entirely based on measurements of serum potassium, degrees of hyperkalaemia and hypokalaemia at various time points and proportion of patients experiencing them. Thus the endpoints are derivatives of one another. Neither urinary nor faecal potassium excretion was studied and levels of other important physiological ions were studied as safety endpoints.

Summary

Following administration of Veltassa, the onset of action was shown to be within 7 hours, and efficacy was persistent with continued dosing through at least 52 weeks, supporting the utility of patiromer powder for oral suspension as a treatment for both acute and chronic hyperkalaemia. Dosing and dose titration were well characterized in these trials and these data support the dosing recommendations for the product labelling. Across the five clinical studies, patiromer powder for oral suspension demonstrated a consistent and reproducible potassium-lowering effect which enabled the majority of subjects to reach and/or remain in the target range with a low risk of hypokalaemia. The proposed starting dose is 8.4 g patiromer, which was the lowest starting dose evaluated in the clinical development program and was associated with statistically significant and clinically meaningful decreases in serum potassium levels. Starting treatment at the lowest effective dose, with titration up to 25.2 g/day patiromer, will result in the majority of patients achieving serum potassium concentrations in the target range while minimizing the risk of hypokalaemia. The pharmacodynamic profile of patiromer powder for oral suspension supports a once daily dosing regimen, which will provide greater convenience for patients and enhance compliance. Once daily dosing will also allow flexibility in dosing times while observing a sufficient separation period (3 hours) between patiromer powder for oral suspension and a potentially interacting concomitant medication. The ability to titrate patiromer powder for oral suspension provides the prescribing clinician flexibility to individualize dosing to achieve larger or smaller potassium reductions in response to changes in the patient's serum potassium levels.

Limitations of the clinical data

Patients with end-stage renal disease (ESRD)

Veltassa has been studied only in a limited number of patients with estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m² and patients receiving dialysis treatment.

Severe hyperkalaemia

There is limited experience in patients with serum potassium concentrations greater than 6.5 mmol/L.

Long term exposure

Clinical trials with Veltassa have not included exposure longer than one year.
The EPAR for Veltassa notes that the patients recruited in the clinical programme had chronic kidney disease; therefore the potassium lowering effects in cases of hyperkalaemia due to other reasons was not studied. However, considering the mechanism of action of Veltassa which is not specific to CKD this uncertainty can be considered negligible. Veltassa was also studied in a limited number of patients with eGFR<15 ml/min/1.73 m^2 and patients receiving dialysis treatment. Further, there is limited experience in patients with serum potassium concentrations greater than 6.5 mmol/L, as a precautionary measure this is outlined in the SmPC.

In the phase III study, patients were dosed twice daily, however, to mitigate the effects of potential binding to other oral medications, the advice in the SmPC is to dose once daily, which could potentially limit the effect of Veltassa when used in clinical practice.

Summary of safety data:

Adverse Events

Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) were reported in 60.8% and 8.3%, respectively,[7] of the pooled safety population receiving patiromer for up to 52 weeks, with a similar proportion in the treatment and prevention studies populations. Approximately 20% of subjects receiving patiromer experienced AEs considered related to study drug, but no SAEs were assessed by either the investigator or sponsor as related to the drug. Number of subjects discontinuing study drug due to an AE was relatively low at 9.0%, indicating the therapy was generally well tolerated, including by those who were treated for up to 1 year in study RLY5016 205. These trends were similar in the treatment and prevention studies.

The majority of the adverse reactions (ARs) reported from trials were gastrointestinal disorders, with the most frequently reported ARs being constipation (6.2%), diarrhoea (3%), abdominal pain (2.9%), flatulence (1.8%) and hypomagnesaemia (5.3%). Gastrointestinal disorder reactions were generally mild to moderate in nature, did not appear to be dose related, generally resolved spontaneously or with treatment, and none were reported as serious. Hypomagnesaemia was mild to moderate, with no patient developing a serum magnesium level <1 mg/dL (0.4 mmol/L).

System Organ Class	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)
Metabolism and nutrition disorders	Hypomagnesaemia	
Gastrointestinal disorders	Constipation Diarrhoea Abdominal pain Flatulence	Nausea Vomiting

The long-term safety database is limited. In the few patients that were dosed up to a year, efficacy was maintained and no safety issues were identified. Patients with a history of bowel obstruction or major gastrointestinal surgery, severe gastrointestinal disorders, or swallowing disorders were not included in the clinical studies. Gastrointestinal ischaemia, necrosis and/or intestinal perforation have been reported with other potassium binders. The benefits and risks of administering Veltassa would therefore need to be carefully evaluated in patients with current or history of severe gastrointestinal disorders, before and during treatment. These uncertainties are sufficiently addressed with routine risk minimisation measures.

Strengths and limitations of the evidence:

Strengths:

- Large number of patients (243) included in Phase 3 trial, over 52 weeks
- A total of 791 subjects participated in the clinical studies with patiromer powder for oral suspension. Of these, 734 were exposed to at least one dose of patiromer, with 149 subjects exposed for ≥ 1 year.
- In the pooled safety population, the AEs that led to permanent discontinuation of patiromer occurred in 60 subjects (9.0%), including 51 subjects (9.3%) treated with patiromer in the treatment studies and 9 subjects (7.6%) treated with patiromer in the prevention studies. The overall frequency for any one individual event leading to drug discontinuation was low (< 2%).

- Across all clinical studies, Veltassa demonstrated a consistent and reproducible potassium-lowering effect which enabled the majority of subjects to reach and/or remain in the target range with a low risk of hypokalaemia

Limitations:

- Most of the studies were single-blind, which can be considered acceptable since plasma potassium measurement is an objective measurement and not likely to be influenced by patient or physician knowledge of the given therapy.
- Most studies were placebo-controlled, there are no active-controlled clinical studies. However, the other main therapies for treatment of hyperkalaemia are sodium polystyrene sulfonate and calcium polystyrene sulfonate. Major limitations of these are tolerability and patient adherence, which limits their use to short durations. They are also contraindicated for patients with serum potassium < 5.0 mEq/L. Therefore it can be argued that due to the frequent stop and start cycles of drug administration which complicates chronic dosing, it would have been difficult to use them as comparators, particularly when evaluating long-term use.
- Twice daily dosing was used whereas licensed dosing is once daily.

Comparison of Calcium Resonium (current treatment option), with Patiromer (proposed treatment option), for the treatment of hyperkalaemia

Calcium Resonium	**Patiromer**
for the treatment of hyperkalaemia associated with anuria or severe oliguria. It is also used to treat hyperkalaemia in patients requiring dialysis and in patients on regular haemodialysis or on prolonged peritoneal dialysis.	indicated for the treatment of hyperkalaemia in adults
The usual dose is 15g **three or four times a day.** **Cost per patient for 30 days = £410.80- £492.96**	The recommended starting dose is 8.4 g patiromer **once daily.** **Cost per patient for 30 days =£300**
Contraindications: **In patients with plasma potassium levels below 5mmol/litre.** • Conditions associated with hypercalcaemia (e.g. hyperparathyroidism, multiple myeloma, sarcoidosis or metastatic carcinoma). • History of hypersensitivity to polystyrene sulfonate resins. • Obstructive bowel disease. • Calcium Resonium should not be administered orally to neonates and is contraindicated in neonates with reduced gut motility (post-operatively or drug-induced). • Hypersensitivity to the active substance or to any of the excipients.	Contraindications: Hypersensitivity to the active substance or to any of the excipients
Undesirable effects: **Metabolism and nutrition disorders** including hypokalaemia, hypercalcaemia and hypomagnesaemia **Gastrointestinal disorders**; Gastric irritation, anorexia, nausea, vomiting, constipation and occasionally diarrhoea may occur. Gastrointestinal stenosis and intestinal obstruction have also been reported. **Gastrointestinal ischemia, ischemic colitis, gastro-intestinal tract ulceration or necrosis, which could lead to intestinal perforation have been reported**. **Respiratory, thoracic and mediastinal disorders**; there have been Some cases of	Undesirable effects: **Metabolism and nutrition disorders**; Hypomagnesaemia was mild to moderate, **Gastrointestinal disorders**; constipation, diarrhoea, abdominal pain, flatulence and hypomagnesaemia have been reported. Gastrointestinal disorder reactions were generally mild to moderate in nature, did not appear to be dose related, generally resolved spontaneously or with treatment, and **none were reported as serious**.

acute bronchitis and/or broncho-pneumonia associated with inhalation of particles of calcium polystyrene sulfonate	
Storage: Shelf life 5 years. Store in a dry place.	Storage: Shelf life 3 years. Store and transport refrigerated (2°C – 8°C). Patients may store Veltassa below 25°C for up to 6 months.

Prescribing and risk management issues:

None identified

Commissioning considerations:

Anticipated patient numbers and net budget impact

Hyperkalemia is defined as a serum potassium level above the reference range and arbitrary thresholds are used to indicate degree of severity, such as >5.0, >5.5 or >6.0 mmol/L.[8] Patients with chronic kidney disease (CKD) (especially advanced CKD) are at high risk for hyperkalemia, especially when other factors and comorbidities that interfere with renal potassium excretion are present. The prevalence of hyperkalemia in CKD patients is considerably higher than in the general population. A recent review reports hyperkalemia frequency as high as 40-50% in the CKD population compared to 2-3% in the general population.[8] Those at highest risk are patients with diabetes and advanced CKD, kidney transplant recipients, and patients treated with renin-angiotensin aldosterone system inhibitors. However, from the prescribing figures obtained for the last year for Calcium Resonium it would appear that the majority of prescribing for hyperkalaemia in Lancashire currently takes place within Secondary care, with only approximately 180 x 300g tubs prescribed in primary care (at a cost of **£14,891.50**) and 5-6 tubs per month being required for each patient (dependent on dose) for long term therapy.

Assuming these prescriptions are for patients on long term therapy we would equate these figures to 3 patients (180÷12= 15tubs / month, 15÷5 tubs / patient =3). If 3 patients were to be prescribed patiromer long term the comparative costs would be £300 x 3 = £900/month, £900 x 12= **£10,800**.

Associated additional costs or available discounts:

None identified

Productivity, service delivery, implementation:

Serum potassium should be monitored when clinically indicated, including after changes are made to medicinal products that affect the serum potassium concentration (e.g. RAAS inhibitors or diuretics) and after the Veltassa dose is titrated.
Serum magnesium should be monitored for at least 1 month after initiating treatment, and magnesium supplementation considered in patients who develop low serum magnesium levels.
Store and transport refrigerated (2°C – 8°C). Patients may store Veltassa below 25°C for up to 6 months. For either storage condition, Veltassa should not be used after the expiry date printed on the sachet.

The mixture should be taken within 1 hour of initial suspension.

Patiromer has the potential to bind some oral co administered medicinal products, which could decrease their gastrointestinal absorption. As precautionary measure, and based on the data summarised below, administration of Veltassa should therefore be separated by at least 3 hours from other oral medicinal products – patient counselling required.

Innovation, need, equity:

Sodium polystyrene sulfonate and calcium polystyrene sulfonate are the two cation-exchange resins currently approved in the UK for the treatment of hyperkalaemia. They were introduced in the 1950s and 1960s; however, have not been rigorously studied. 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. The usual oral dose is 15g three or four times a day, the resin may also be given rectally as a suspension of 30g resin in 150ml of water or 10% dextrose, as a daily retention enema.

Both calcium and sodium polystyrene sulfonate are contraindicated for treating patients with a serum potassium < 5.0 mEq/L and both require frequent stop and start cycles of drug administration, further complicating chronic dosing. Thus, there is a need for new therapies for hyperkalaemia whose efficacy and safety are well characterized and can be administered long term with once daily dosing.

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: high quality randomised controlled trials (RCTs) with low risk of bias systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: clinical trials at moderate or high risk of bias systematic reviews or meta-analyses of such clinical trials or with inconsistent findings cohort studies case-control studies	
Level 3	Disease-oriented evidence, or evidence from: consensus guidelines expert opinion case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

Midlands and Lancashire Commissioning Support Unit,
Jubilee House, Lancashire Business Park, Leyland, PR26 6TR

References

1) Weir M R et al; Patiromer in Patients with Kidney Disease and Hyperkalemia Receiving RAAS Inhibitors. The New England Journal of Medicine January 15, 2015 vol. 372 no. 3

2) 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):151-161.

3) SPC Veltassa (Patiromer) https://www.medicines.org.uk/emc/medicine/33866 accessed online October 2017

4) SPC Resonium A https://www.medicines.org.uk/emc/medicine/6988 accessed online October 2017

5) SMPC Calcium Resonium 99.934% w/w Powder for Oral/Rectal Suspension https://www.medicines.org.uk/emc/medicine/6739 accessed online October 2017

6) BNF 72 September 2016-March 2017

7) EMA assessment report Veltassa 18 May 2017 EMA/CHMP/424270/2017

8) Kovesdy CP. Management of hyperkalaemia in chronic kidney disease. Nat Rev Nephrol. 2014 Sep 16