In this product focus, Dr Robert Lewis details how patiromer, a non-absorbed polymer, can appropriately and effectively be used to treat patients with chronic kidney disease, heart failure and diabetes mellitus.

### Abstract

Patiromer is a recently introduced non-absorbable polymer that is taken orally in suspension to bind potassium in the intestine, thereby reducing its absorption. It has been shown to be well tolerated and effective, both in the treatment of acute hyperkalaemia and to manage persistent hyperkalaemia. This article will detail only the latter circumstance, focusing on the potential role of patiromer in optimising long-term medical therapy for patients with chronic kidney disease, heart failure and diabetes. The mechanism of action of patiromer in vivo will be explained, and the results of clinical trials that have established its clinical utility will be reviewed. Finally, how and when this agent should be used in clinical practice will be described, with reference to recent best practice guidelines.

### How the body handles potassium

A typical western diet has a daily potassium content of 20–90 mmols. Approximately 10% is lost in the faeces, and the rest is absorbed by the gut, along with about 6 litres per day of fluid (containing approximately 15 mmols/l of potassium) that is secreted by the intestine to enhance digestion. A small amount of the absorbed potassium is retained by the kidneys to replace daily losses (for example, sweat), and the rest is excreted in the urine. Renal potassium loss at the distal tubule is controlled by aldosterone, the secretion of which increases when blood potassium levels rise. By these means, and there is an association between sustained high potassium levels and increased mortality in patients with diabetes mellitus (DM), chronic kidney disease (CKD) and heart failure (HF) (Figure 1) (Collins et al, 2017). Furthermore, therapies that are frequently used in these conditions contribute to the development of hyperkalaemia. This limits their clinical use, and is thus a barrier to optimal care, which may have an adverse impact on patient outcomes.

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the serum potassium is normally tightly regulated between 3.5–5 mmols/l.

The body uses potassium to establish electrical gradients and flows between the extracellular and intracellular spaces, thereby regulating resting membrane potential and cellular excitability. This is essential for the normal function of excitable tissues, such as nerves, muscles and cardiac conduction tissues. Generation of these electrical gradients relies on plasma membrane Na-K-ATPases, which pump sodium out of cells in exchange for potassium and maintain an intracellular potassium level that far exceeds that in the extracellular compartment. A person weighing 70 kg has a total of approximately 3500 mmols potassium in their body, of which, only 70 mmols (2%) is extracellular. The amount of potassium that is pumped from the extracellular fluid into the cells is increased by insulin, beta2-adrenergic activity and low H+ concentrations (alkalosis) (Palmer, 2010). Therefore, these factors have a role in determining the amount of potassium in the extracellular compartment, and, thus, the amount circulating in the blood.

A high concentration of potassium in the extracellular fluid (as occurs during hyperkalaemia) reduces the difference between intracellular and extracellular potassium concentrations, thus reducing the electrical potential across cell membranes. The resultant reduction in membrane excitability explains the clinical consequences of hyperkalaemia: in the heart, this includes heart block and arrhythmias (including asystole) and, in skeletal muscle, flaccid muscle paralysis. These effects occur abruptly when the serum potassium exceeds a critical threshold. Where this threshold lies differs from one individual to another, and there are no prodromal symptoms. Accordingly, it is impossible to know with any certainty when a patient with hyperkalaemia will come to harm; one can only measure the serum potassium and use this as a means of assessing risk—the higher that it is, the greater the risk and the greater the need for remedial action.

Why persistent hyperkalaemia occurs in cardiorenal disease

Although there are many conditions that may be associated with chronic persistent hyperkalaemia, there are three that are especially important in clinical practice: CKD, HF and DM. These conditions often occur together—approximately 50% of people with HF have renal dysfunction (Lofman et al, 2016), while people with CKD have three-times the risk for developing HF than the general population (Kottgen et al, 2007). HF is the most common cardiovascular comorbidity in type 2 diabetes (Rosano et al, 2017), and diabetes is the cause of renal failure in approximately 30% of people receiving renal replacement therapy (UK Renal Registry, 2020).

CKD predisposes to the development of hyperkalaemia due to impaired potassium clearance, reduced responsiveness to aldosterone and metabolic acidosis. Diabetes compounds these effects through low insulin levels and hyperglycaemia (and resultant plasma hyperosmolality), both of which cause potassium to move out of cells and...
into the extracellular compartment. This tendency towards hyperkalaemia in HF, CKD and DM is further augmented by the medicines that are used in managing these conditions.

Management of heart failure

Angiotensin-converting enzyme (ACE) inhibitors are widely used in the treatment of heart failure. These agents decrease the formation of angiotensin II, thereby decreasing both arteriolar and venous resistance. This vasodilator effect causes immediate improvement in the symptoms of heart failure by decreasing left ventricular afterload. ACE inhibitors also slow the rate of progression of cardiac dysfunction, with a 25% reduction in cardiovascular mortality at 1–3 years (CONSENSUS Trial Study Group, 1987). Additionally, the administration of ACE inhibitors after an acute myocardial infarction can preserve cardiac function and improve long-term survival (Pfeffer et al, 1992). The addition of a beta-blocker to initial therapy with ACE inhibitors can reduce mortality and admissions to hospital by a further 30% (Foody et al, 2002).

The European Society of Cardiology’s guidelines for management of heart failure (2016) recommend ACE inhibitors and beta-blockers as first-line treatments, with the ACE inhibitor titrated to the highest tolerable dose to obtain the greatest benefit. If this combination does not improve symptoms, the guidelines recommend the addition of a mineralocorticoid receptor antagonist (MRA), which can improve symptoms and further reduce mortality by 25%. Use of angiotensin receptor blockers (ARBs) may be used as an alternative to ACE-inhibitors if the latter are not tolerated. (European Society of Cardiology, 2016). ACE inhibitors, ARBs, beta-blockers and MRAs all increase serum potassium levels, particularly when used in combination for optimal therapy. The incidence of hyperkalaemia in HF is therefore high, reaching 40% in some series (Thomsen et al, 2018).

Management of chronic kidney disease and diabetic nephropathy

Agents inhibiting the renin angiotensin aldosterone system (RAAS) reduce intraglomerular hypertension, which is considered to be a key contributor to the progression of CKD (Matovinović, 2009). ACE inhibitors and ARBs reduce proteinuria in people with CKD of any cause, and this is associated with improved renal prognosis (Jafar et al, 2001). People with diabetic nephropathy who received an ARB to control their blood pressure have shown a 28% slowing in CKD progression compared with a cohort whose blood pressure was equally controlled (Brenner et al, 2001). People with diabetic nephropathy who received an ARB to control their blood pressure have shown a 28% slowing in CKD progression compared with a cohort whose blood pressure was equally controlled (Brenner et al, 2001). Drugs acting on the RAAS have a renoprotective effect, which is in addition to any benefit from lowering blood pressure. Accordingly, guidelines for the management of CKD—including those that were produced by the National Institute
for Health and Care Excellence (NICE) (2015)—recommend the use of an ACE inhibitor or ARB as the first-line treatment for people with:
- DM and an albumin creatinine ratio (ACR) >3 mg/mmol
- Hypertension and an ACR >30 mg/mmol
- ACR >70mg/mmol, regardless of blood pressure.
As the renoprotective effects of these drugs are dose-dependent, it is recommended that drugs blocking the RAAS should be used at higher doses. A recent study has shown that the addition of the MRA finerenone to people with diabetic nephropathy who are receiving optimal treatment with an ACE inhibitor or ARB can further improve renal outcomes (Bakris et al, 2020); however, the place of MRAs in the management of CKD has yet to be fully established.

Therefore, agents acting on the RAAS and prescribed at high doses are the mainstay of symptom control and risk reduction in people with HF, CKD and DM. As previously noted, the pathophysiology of these conditions predisposes to high blood potassium levels. Consequently, the additional potassium retention due to RAAS blockade greatly increases the risk of developing clinically important hyperkalaemia.

### Overcoming the obstacle of persistent hyperkalaemia

When optimal treatment of CKD, HF or DM leads to hyperkalaemia, at times, the problem can be addressed with dietary potassium restriction. Patients may be able to manage this themselves using readily available diet sheets, but long-term adherence...
is often burdensome. Reliable dietary potassium control usually requires advice, encouragement and monitoring by a suitably trained dietician, which necessitates further clinical input. Coadministration of diuretics (which increase urinary potassium loss) can control potassium but should not be given solely for this purpose due to the risk of hypovolaemia. When acidosis is present, correcting it with oral sodium bicarbonate may usefully lower serum potassium levels. However, because the major contributor to hyperkalaemia is the administration of drugs acting on the RAAS, the option of reducing or stopping them is often taken by clinicians on the principle of primum non nocere. To do so costs the patient the beneficial effects of these medicines on disease progression, which were described earlier. One retrospective study showed that hyperkalaemia (K >5.5 mmol/L) led to a clinical decision to reduce RAAS blockade to suboptimal doses, or stop it completely, in approximately 50% of people and that, over 5 years, this group had double the mortality of people who remained on an optimal dose (Figure 2) (Epstein et al, 2015).

An alternative strategy is to maintain RAAS blockade at doses that accord with recommended best practice, while treating or avoiding hyperkalaemia by using an additional agent that is designed to reduce blood potassium. Potassium binders, such as calcium polystyrene sulphonate (CPS) and sodium polystyrene sulphonate (SPS), have been available for decades, but they have proved to be too poorly tolerated by patients to provide a solution to the problem. They are unpalatable to take and cause intrusive gastrointestinal side effects, including constipation, nausea and, in rare cases, intestinal necrosis (Harel et al, 2013). In a study of approximately 4500 patients initiating therapy with SPS, only 49.8% continued treatment for more than 7 days and less than 10% continued for more than 60 days (Bets et al, 2016).

Now, two agents (sodium zirconium cyclosilicate (SZC) and patiromer) have become available that do not appear to have the same severe gastrointestinal tolerability concerns, and, therefore, may provide a new approach to controlling persistent hyperkalaemia, thereby allowing appropriate optimisation of RAAS inhibition.

SZC is an inorganic, unabsorbable non-polymeric compound that is dissolved in water and taken orally. The ion channels that are formed by the atomic structure of SZC mimic those of endogenous potassium channels and have a pore diameter of 3 Å, which is similar to the size of a potassium ion (2.98 Å). When the sodium ion dissociates from SZC in the solution, the negative charge created preferentially traps potassium. Accordingly, SZC is 25-times more selective for potassium than calcium or magnesium (Stavros et al, 2014). SZC has been shown to be effective in lowering serum potassium in people with hyperkalaemia, who may benefit from continuation of RAAS blockade. The HARMONIZE study evaluated the effect of SZC at various doses on potassium-lowering at 48 hours and at 28 days in subjects with CKD, diabetes and heart failure (74.5%, 60% and 40% of participants, respectively) with hyperkalaemia (K >5.1 mmol/L), most of whom were taking RAAS blockers (67% of participants) (Roger, 2019). SZC maintained normokalaemia in 71–85% of participants (depending on SZC dose). A non-randomised extension to the study showed that normokalaemia could be maintained for 1 year in 88% of eligible patients. The agent was generally well tolerated by subjects, although dose-related oedema was reported.

The mechanism of action of patiromer is different from SZC. It is a spherical non-absorbed polymer that binds potassium in the gut in a similar way to SPS, but with much greater affinity (Li et al, 2016). It has improved physical properties, such as a low swelling ratio, which may improve its tolerability for patients. Patiromer uses calcium-sorbitol, rather than sodium, as the exchange cation, and is designed to be fully ionised at the physiological pH of the colon, thereby optimising ion exchange where the concentration of potassium in the GI tract is the highest. Patiromer begins to affect blood potassium levels approximately 4–7 hours after dosing (Bushinsky et al, 2015).

**Clinical trials and patiromer**
Patiromer has been shown to be an effective treatment for persistent hyperkalaemia. Phase 2 and 3 clinical trials involving patiromer are summarised in Table 1. The PEARL-HF trial demonstrated that, in patients with heart failure, patiromer can control potassium, allowing maintenance of MRA therapy (Pitt et al, 2011). The AMETHYST-DN study showed that patiromer effectively controlled serum potassium levels in diabetic patients with CKD and hyperkalaemia receiving an ACE inhibitor, ARB or both, often in combination with spironolactone (Bakris et al, 2015). Continued treatment with patiromer controlled potassium for up to 52 weeks, whereas withdrawal of patiromer resulted in a prompt increase in the serum potassium. The OPAL-HK study showed that hyperkalaemia of different severities could be controlled at 4 weeks by a range of patiromer doses (Weir et al, 2015). Patients reaching normokalaemia were then randomised to continue patiromer or receive a placebo. Some 8 weeks later, those on patiromer...
maintained normokalaemia, whereas potassium rose significantly in the placebo group. Patiromer was well tolerated during these studies; the adverse events reported included gastrointestinal effects (nausea, constipation), hypokalaemia (which can be addressed by dose reduction) and hypomagnesaemia.

Where patiromer fits into best practice guidelines

Patiromer has undergone a technical appraisal by NICE (NICE, 2020). With specific regard to the management of persistent hyperkalaemia, NICE recommended patiromer as a treatment option in adults with stages 3b–5 CKD or HF if they have a confirmed serum potassium level of at least 6.0 mmol/l, are either not taking, or are taking a reduced dosage of, a RAAS inhibitor because of hyperkalaemia and are not on dialysis.

The same recommendation was applied to SZC after a similar NICE technical appraisal (NICE, 2019). However, it is noteworthy that NICE’s guidelines for management of CKD still recommend stopping drugs acting on the RAAS when the serum potassium exceeds 6 mmols/l (NICE, 2015). It remains to be seen if this apparent inconsistency will be addressed in an imminent revision of NICE guidance.

Guidelines for the management of hyperkalaemia have recently been produced by the Renal Association (2020). In line with the NICE technical appraisal, the guidelines recommend that patiromer and SZC should be considered as options for the management of persistent hyperkalaemia with a confirmed serum K+ ≥6.0 mmol/l in patients with CKD stage 3b–5 (not on dialysis) or HF who are receiving a suboptimal dose of RAAS inhibitor therapy. The Renal Association’s guidelines also recommend that the decision to start these agents should be made in secondary care. Therefore, a transfer of care arrangement needs to be put into place for subsequent prescriptions to be issued in the community by general practitioners—a so-called ‘amber’ rating in the traffic light system that is used by NHS prescribing authorities.

As patiromer is a relatively recent introduction, it is yet to find its place in international management guidelines. However, there is increasing acceptance that managing hyperkalaemia by simply reducing RAAS blockade may not be best practice. For instance, Kidney Disease: Improving Global Outcomes (KDIGO) states that, if patients who are receiving RAAS blockade develop hyperkalaemia, management should include consideration of ‘Gliclazide exchangers’ and reduction or cessation of RAAS blockade should be a ‘last resort’ (KDIGO, 2020).

Key points

- Agents inhibiting the renin angiotensin aldosterone system (RAAS) are the mainstay of optimal long-term management of chronic kidney disease, heart failure and diabetic kidney disease
- Hyperkalaemia is common in these conditions, occurring in 40% of people with advanced diabetic kidney disease
- Hyperkalaemia is frequently managed by reducing or stopping medicines that block the RAAS, thereby leading to suboptimal treatment
- Clinical trials have shown that potassium binders, such as patiromer, are effective and well tolerated, providing an alternative means of managing hyperkalaemia in people receiving RAAS blockade
- These agents are approved by the National Institute for Health and Care Excellence and endorsed by the Renal Association for managing hyperkalaemia in high-risk patients with cardiorenal disease.

Using patiromer in clinical practice

Patiromer presents as a sachet of powder that should be mixed in an initial volume of 40 ml water in a clean glass and stirred, with more water added to obtain the desired consistency (Electronic Medicines Compendium, 2020). It remains in suspension as a cloudy liquid. The mixture should be consumed within 1 hour of initial suspension and is not affected by food. As it binds certain drugs in the gut (including ciprofloxacin, thyroxine and metformin), administration of patiromer should be separated by 3 hours from other oral medicinal products (Electronic Medicines Compendium, 2020).

Based on the aforementioned large trials, patiromer is recommended at a starting dose of 8.4 g once daily, which can be increased by 8.4g increments per week, titrated up to a maximum of 25.2 g once daily. There is no consensus on how often blood tests should be performed while taking patiromer. It is recommended that an initial serum potassium check is performed 7 days after starting patiromer treatment, and that the serum magnesium level is checked after approximately 1 month. Thereafter, the frequency of testing depends on the individual clinical circumstances. The risks posed by the COVID-19 pandemic to people with important comorbidities attending for blood tests should be taken into account. Once stable blood potassium has been attained, these should be minimised.

Conclusions

Numerous studies have shown that optimal management of CKD, HF and DM should include the use of agents that act on the RAAS in high doses. This endeavour is limited by hyperkalaemia, which can have serious consequences for patients. Compared with older potassium binders, patiromer is well tolerated and convenient for the patient to use. It has been approved by NICE in certain defined circumstances and is endorsed as an option in the
Renal Association guidelines on the management of hyperkalaemia. Accordingly, clinicians are no longer required to reduce or stop RAAS blockade to control potassium at safe levels; they have the option of using potassium binding agents such as patiromer to maintain RAAS blockade at doses that have a proven benefit. Studies are now required to demonstrate the effect of using these agents on long-term clinical outcomes in people being treated for cardiorenal disease.

References


Veltassa® (patiromer sorbitex calcium)
Prescribing Information – United Kingdom

For full prescribing information refer to the Summary of Product Characteristics (SmPC)

Active ingredient: patiromer sorbitex calcium
Presentation Powder for oral suspension available in sachets containing either 8.4g, 16.8g.

Indication: Treatment of hyperkalaemia in adults.

Dosage and Administration: The recommended starting dose is 8.4 g administered orally once daily with or without food. The daily dose may be adjusted by 8.4 g as needed at one-week intervals or longer to reach desired serum potassium 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 and 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 occurs 4–7 hours after administration. Veltassa should not replace emergency treatment for life-threatening hyperkalaemia.
There is limited data on the use of Veltassa in patients on dialysis; no special dose and administration guidelines were applied to these patients in clinical studies. The complete dose should be poured into a glass containing approximately 40 ml of water, then stirred. Another approximately 40 ml of water should be added. And the suspension stirred again thoroughly. More water may be added to the mixture as needed for desired consistency. The mixture should be taken within 1 hour. Apple juice and cranberry juice can be used instead of water to prepare the mixture. Other liquids with high potassium content should be avoided.

Contraindications: Hypersensitivity to active ingredient or to the excipient xanthan gum.
Special warnings and precautions: 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. A risk/benefit evaluation is required in patients with current or a history of severe gastrointestinal disorders, before and during treatment. When discontinuing Veltassa, serum potassium levels may rise, especially if RAAS inhibitor treatment is continued, so patients should be instructed not to discontinue therapy without consulting their physicians. Increases in serum potassium may occur as early as 2 days after the last dose. 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 dose titration. Veltassa contains sorbitol as part of the counterion complex (4 g per 8.4 g of patiromer), therefore patients with hereditary problems of fructose intolerance should not take this medicine. Veltassa contains calcium as part of the counterion complex; calcium is partially released, some of which may be absorbed therefore a risk/benefit evaluation is required in patients at risk of hypercalcaemia. There are limited clinical data in patients with end-stage renal disease and in patients with serum potassium concentrations greater than 6.5 mmol/L.

Overdose: Veltassa is excreted after approximately 24–48 hours, based on average gastrointestinal transit time. Excessive doses may result in hypokalaemia, therefore serum potassium levels should be monitored.
Special populations: The use of Veltassa has not been studied in children under 18 years. Since there are no data from the use of patiromer in pregnant women, it is preferable to avoid the use of Veltassa during pregnancy. No special dose and administration guidelines are recommended for elderly population.

Undesirable effects: Common (≥1/10 to <1/10): Hypomagnesaemia, constipation, diarrhoea, abdominal pain, flatulence. Please consult the SmPC in relation to other undesirable effects.

Legal category: POM
Price: pack of 30 x 8.4g sachets = £172.50; pack of 30 x 16.8g sachets = £345.00
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Date of Authorisation: 19/07/2017
MA Holder: Vifor Fresenius Medical Care Renal Pharma France, 100-101 Terrasse Boieldieu, Tour Franklin La Défense 8, 92042 Paris La Défense Cedex, France

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