

1. NAME OF THE MEDICINAL PRODUCT

Veltassa 8.4 g powder for oral suspension
Veltassa 16.8 g powder for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains 8.4 g patiomer (as patiomer sorbitol calcium (patiomer sorbitex calcium))
Each sachet contains 16.8 g patiomer (as patiomer sorbitol calcium (patiomer sorbitex calcium))

The sorbitol content is 3.765 g in the 8.4 g sachet and 7.53 g in the 16.8 g sachet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for oral suspension.
Off-white to light-brown powder, occasionally containing white particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Veltassa is indicated for the treatment of hyperkalaemia in adults.

4.2 Posology and method of administration

Posology

Initiation of therapy

The recommended starting dose is at least 8.4 g of patiomer once a day.

In general, administration of Veltassa should be separated by 3 hours from other oral medicinal products. Separation is not needed for certain medicinal products (see section 4.5).

Because of delayed onset of action, Veltassa should not replace emergency treatment for life-threatening hyperkalaemia.

Dosage adjustment and maintenance therapy

The daily dose of Veltassa should be adjusted based on potassium level and desired target range. The daily dose may be increased or decreased by intervals of one week in increments of 8.4 g as needed to reach the desired target range, up to a maximum daily dose of 25.2 g. Multiple sachets may be used to achieve the desired dose. If the potassium level falls below the desired target range, administration of Veltassa should be reduced or discontinued.

If a dose of Veltassa is forgotten, the forgotten dose should be taken as soon as possible on the same day. The forgotten dose should not be taken with the following dose.

Method of administration

Oral use.

Veltassa should be mixed with water or other fluids or soft foods listed below until a uniform consistency is achieved, according to the following steps:

The entire dose of Veltassa should be first mixed with approximately 40 mL of water (3 tablespoons) in a glass. Then add approximately 40 mL of water and carefully mix the suspension. The powder will not dissolve. If necessary, water can be added to the mixture to obtain the desired consistency.

The mixture should be consumed immediately. If powder remains in the glass after consuming the mixture, add water, mix and drink immediately. Repeat if necessary to guarantee administration of the entire dose.

The following liquids or soft foods can be used instead of water to prepare the mixture by following the same steps as described above: apple juice, cranberry juice, pineapple juice, orange juice, grape juice, pear juice, apricot nectar, peach nectar, yoghurt, milk, thickener, apple sauce, vanilla and chocolate pudding.

The potassium content of liquids or soft foods used to prepare the mixture should be considered as part of the dietary recommendations on potassium intake for each individual patient.

Veltassa can be taken with or without food. Veltassa should not be heated (for example in a microwave) or added to hot food or beverages. Veltassa should not be taken in its dry form.

Special dosing instructions

Dialysis patients

There is only limited data available on the use of Veltassa in dialysis patients. No specific guidelines for dose and administration were applied to these six patients during clinical studies.

Elderly patients

Among the total number of patients treated with Veltassa during clinical trials, 1,307 (61.2%) patients were 65 years and older, and of these patients, 500 (23.4%) were 75 years and older. No specific dose guidelines were applied in these patients during these studies.

Children and adolescents

The safety and efficacy of Veltassa in children and adolescents aged up to 18 years have not yet been established. No data are available.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Hypomagnesaemia

Patiromer may cause hypomagnesaemia by binding magnesium in the colon. In clinical studies, magnesium levels <1.4 mg/dL were observed in 7.1% of patients treated with Veltassa, with 0.3% of patients developing magnesium levels <1.0 mg/dL. Mean reductions in magnesium level occurred at the start of treatment with Veltassa and were ≤ 0.118 mg/dL one week after the start of treatment with Veltassa. Magnesium levels must be monitored for one month after

initiating treatment with Veltassa and monitoring should be continued in the event of decreased serum levels of magnesium. Magnesium supplementation should be planned in patients who develop hypomagnesaemia during treatment with Veltassa.

Gastrointestinal disorders

Patients with a history of intestinal blockage or major digestive surgery, diabetic gastroparesis, presenting severe gastrointestinal disorders or swallowing disorders were not included in the clinical studies. Treatment with Veltassa should be avoided in these patients.

Discontinuation of treatment with Veltassa

Potassium levels may increase upon discontinuation of treatment with Veltassa, particularly in cases where treatment is followed by a renin angiotensin aldosterone system (RAAS) inhibitor. Patients should be informed that they must not discontinue treatment without consulting their doctor. Increases in potassium level may occur starting from the 2nd day after the last dose of Veltassa.

Serum potassium levels

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.

Sorbitol

Veltassa contains sorbitol as part of the counterion complex. The sorbitol content is approximately 4 g (10.4 kcal) per 8.4 g of patiomer. Patients presenting a hereditary intolerance to fructose (HFI) must not take/receive this medicinal product.

Fluoride

Veltassa contains fluoride. In patients presenting severe chronic renal insufficiency (CRI), all other sources of fluoride should be limited.

Information about calcium

Veltassa contains calcium as part of the counterion complex. Calcium is partially released some of which may be absorbed (see section 5.1). However, in clinical studies with durations up to one year, no meaningful changes in mean serum calcium levels were observed. The benefits and risks of administering this medicinal product should be carefully evaluated by the physician in at risk patients.

4.5 Interaction with other medicinal products and other forms of interaction

Veltassa has the potential to bind certain medicinal products co-administered by oral route, which may reduce their gastrointestinal absorption. As patiomer is not absorbed or metabolised by the body, there are limited effects on the function of other medicinal products.

Table 1 shows the medicinal products tested for interactions with Veltassa and recommendations for administration of these medicinal products with Veltassa. For oral medicinal products not listed, administration of patiomer should be separated by at least 3 hours as precautionary measure.

Table 1: Recommendations for administration of medicinal products tested for interactions with Veltassa

Medicinal product		Clinical recommendation	Basis for recommendation
	Angiotensin-converting enzyme (ACE) inhibitors		
Benazepril, captopril, enalapril, fosinopril, lisinopril, perindopril, quinapril, ramipril, trandolapril		No separation from Veltassa required	In vitro: no interaction observed
	Angiotensin II receptor blockers (ARB)		
Telmisartan		Separate by at least 3 hours from Veltassa	In vitro binding observed
Azilsartan, candesartan, irbesartan, losartan, olmesartan, valsartan		No separation from Veltassa required	In vitro: no interaction observed
	β-adrenoceptor blockers (β-blocker)		
Bisoprolol, carvedilol, nebivolol		Separate by at least 3 hours from Veltassa	In vitro binding observed
Metoprolol		No separation from Veltassa required	In vivo: no interaction observed
	Loop diuretics		
Furosemide		No separation from Veltassa required	In vivo: no interaction observed
Bumetanide, torasemide			In vitro: no interaction observed

	Mineralocorticoid receptor antagonists (MRA)		
Eplerenone, finerenone, spironolactone		No separation from Veltassa required	In vitro: no interaction observed
	Neprilysin inhibitors		
Sacubitril		No separation from Veltassa required	In vitro: no interaction observed
	Sodium-glucose cotransporter-2 (SGLT-2) inhibitors		
Canagliflozin, dapagliflozin, empagliflozin		No separation from Veltassa required	In vitro: no interaction observed
	Antibiotics		
Ciprofloxacin		Separate by at least 3 hours from Veltassa	In vivo interactions observed but not when separated by 3 hours
Trimethoprim		No separation from Veltassa required	In vivo: no interaction observed
Amoxicillin, cephalexin			In vitro: no interaction observed
	Anticoagulants		
Warfarin		No separation from Veltassa required	In vivo: no interaction observed
Apixaban, rivaroxaban			In vitro: no interaction observed

	Anti-Parathyroid Agents and Thyroid Preparations		
Levothyroxine		Separate by at least 3 hours from Veltassa	In vivo interactions observed but not when separated by 3 hours
Cinacalcet		No separation from Veltassa required	In vivo: no interaction observed
	Antithrombotic Agents		
Clopidogrel		No separation from Veltassa required	In vivo: no interaction observed
Acetylsalicylic acid			In vitro: no interaction observed
	Blood Glucose Lowering Drugs		
Metformin		Separate by at least 3 hours from Veltassa	In vivo interactions observed but not when separated by 3 hours
Glipizide		No separation from Veltassa required	In vitro: no interaction observed
	Calcium Channel Blockers		
Amlodipine, verapamil		No separation from Veltassa required	In vivo: no interaction observed
	Immunosuppressants		
Mycophenolate mofetil		Separate by at least 3 hours from Veltassa	In vitro binding observed
Tacrolimus		No separation from Veltassa required	In vitro: no interaction observed

	Others		
Quinidine		Separate by at least 3 hours from Veltassa	In vitro binding observed
Lithium		No separation from Veltassa required	In vivo: no interaction observed
Allopurinol, atorvastatin, digoxin, phenytoin, riboflavin, sevelamer			In vitro: no interaction observed

Effect of Food on Veltassa

In an open-label study, 114 patients with hyperkalaemia were randomized to patiromer once daily with food or without food. Serum potassium at the end of treatment, the change from baseline in serum potassium, and the mean dose of patiromer were similar between groups.

4.6 Fertility, pregnancy and lactation

Pregnancy

To date, there are no clinical data regarding the use of Veltassa in pregnant women.

Animal studies have not shown any direct or indirect toxicity affecting pregnancy, embryonic development, foetal development and/or postnatal development (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of Veltassa during pregnancy.

Breastfeeding

No effect on the breastfeeding newborn infant is expected since the systemic exposure to patiromer in breastfeeding woman is negligible. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from patiromer therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility

There are no data on the effect of patiromer on fertility in humans. Animal studies showed no effects on reproductive function or fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Veltassa has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Veltassa's safety profile is based on a total of 2,135 patients having participated in clinical studies and on post-marketing experience.

The majority of the adverse reactions (AR) reported were hypomagnesaemia and gastrointestinal disorders, with the most frequently reported ARs being: constipation, diarrhoea, abdominal pain, nausea, flatulence, vomiting and hypersensitivity. Gastrointestinal disorders were generally of a mild to moderate intensity, did not appear to be dose-dependent, generally resolved spontaneously or with treatment and none were described as serious. The hypersensitivity reactions included skin rashes, urticaria, swelling in the oral cavity and on the lips, and were mild to moderate.

Note: Diarrhoea is an umbrella term for diarrhoea and frequent defaecation. Abdominal pain is an umbrella term encompassing the preferred terms of abdominal complaints, abdominal pain and upper abdominal pain. Constipation is an umbrella term encompassing the preferred terms of constipation and hard stools.

Tabulated list of adverse reactions

Adverse reactions are listed below by system organ class and by frequency.

Frequencies of undesirable effects: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	Common ($\geq 1/100$ to $< 1/10$)	Uncommon ($\geq 1/1,000$ to $< 1/100$)	Not known (cannot be estimated from the available data)
Immune system disorders			Hypersensitivity
Metabolism and nutrition disorders	Hypomagnesaemia		
Gastrointestinal disorders	Constipation Diarrhoea Abdominal pain Nausea Flatulence	Vomiting	

To report any side effect(s):

- The National Pharmacovigilance Centre (NPC):
 - SFDA Call Center: 19999
 - E-mail: npc.drug@sfd.gov.sa
 - Website: <https://ade.sfd.gov.sa/>

4.9 Overdose

Doses of Veltassa greater than 50.4 g of patiromer per day have not been studied. As excessive doses of Veltassa may cause hypokalaemia, serum potassium levels must be monitored. If medical proves necessary, appropriate measures to re-establish normal potassium levels should be undertaken.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for treatment of hyperkalaemia and hyperphosphataemia.

ATC code: V03AE09

Mechanism of action

Veltassa is a non-absorbed, cation exchange polymer that contains a calcium-sorbitol complex as a counterion.

Veltassa increases faecal potassium excretion through binding of potassium in the lumen of the gastrointestinal tract. The binding of potassium reduces the concentration of free potassium in the gastrointestinal lumen, which results in a reduction of serum potassium levels.

Pharmacodynamics

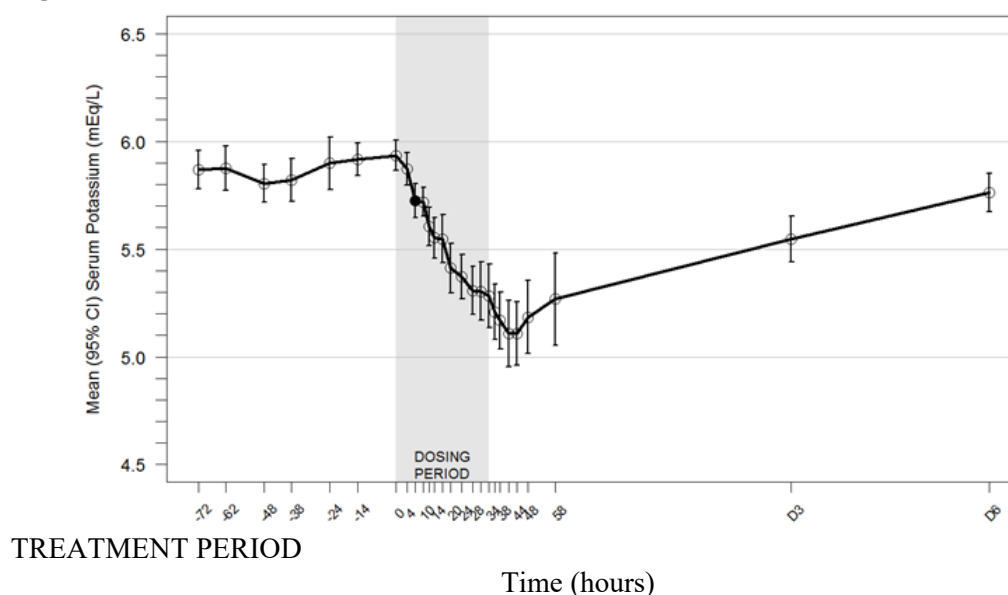
It has been shown that Veltassa binds potassium *in vitro* and *in vivo* in experimental animal models.

In a phase 1 study conducted in healthy adult volunteers (6-8 subjects per group), Veltassa (from 0 g to 50.4 g of patiomer daily) administered three times daily for 8 days induced a dose-dependent increase in faecal excretion of potassium. A corresponding dose-dependent decrease in kaliuresis without effect on serum potassium was also observed. Compared to placebo, Veltassa at doses of 25.2 g and 50.4 g daily significantly reduced mean daily kaliuresis.

In a phase 1, open label, repeat dose crossover study conducted among 12 healthy volunteers, the dose of 25.2 g of patiomer daily was orally administered following a schedule of once a day, twice a day or three times a day for 6 days according to a randomly assigned sequence. A significant increase in mean daily faecal excretion of potassium and a concomitant decrease in mean daily kaliuresis was observed with the three dosing schedules. The mean increase in faecal excretion of potassium was from 1,283 to 1,550 mg/day and mean decrease in kaliuresis was from 1,438 to 1,534 mg/day across the three dosage schedules. No significant difference was observed between the dosing schedules in terms of mean daily faecal and urinary excretion of potassium, either in the global comparison or paired comparison. Daily urinary excretion of calcium increased by 53 mg/day, 66 mg/day and 73 mg/day compared to baseline with the schedules once daily, twice daily and three times daily, respectively.

In a non-controlled, open-label study, 25 patients presenting with hyperkalaemia (mean baseline potassium level of 5.9 mEq/L) and chronic renal insufficiency followed a controlled potassium regimen for three days, then received 16.8 g of patiomer per day (in two fractionated doses) for two days, while continuing the controlled regimen. A statistically significant reduction in potassium levels (0.2 mEq/L) was observed 7 hours after the initial dose. Potassium levels continued to decline during the 48-hour treatment period (0.8 mEq/L 48 hours after initial dose). Potassium levels remained stable for 24 hours following the last dose, then increased during the 4-day observation period following discontinuation of Veltassa.

Figure 1: Onset of action – Mean potassium level (95% CI) (mEq/L) over time



* The full circle indicates the time at which the first statistically significant reduction was identified. A mean reduction of 0.8 mEq/L was observed at hour 48 ($p < 0.001$).

Comments: hours 72 to 0 = pre-screening period with controlled potassium regimen; hours 0 to 58 = period of treatment with Veltassa 16.8 g per day in fractionated doses in a hospital environment; hour 58 to day 6 = period of outpatient follow-up.

Clinical efficacy and safety

The potassium-lowering effect of patiomer has been proven in 5 clinical studies with the participation of patients with hyperkalaemia or normokalaemic patients who received RAASi inhibitors and thus were at an increased risk of hyperkalaemia. The effect of patiomer on hyperkalaemic patients with chronic renal disease who received RAASi inhibitors was examined in a single-blind study with subsequent randomised withdrawal part. An open 52-week study was conducted with hyperkalaemic patients with chronic kidney disease, uncontrolled high blood pressure and type 2 diabetes mellitus who received RAASi inhibitors. In two randomised, double-blind, placebo-controlled studies, patiomer was examined on normokalaemic patients with heart failure or chronic kidney disease and resistant high blood pressure, or during simultaneous start of treatment with RAASi inhibitors (spironolactone). In a double-blind, placebo-controlled study, patients with heart failure and reduced ejection fraction were included who had hyperkalaemia or recently occurring hyperkalaemia and who were able to use and maintain the approved doses of RAASi inhibitors and to achieve or maintain normokalaemia during patiomer intake. Afterwards, the effect of patiomer on the serum potassium level was examined in a randomised withdrawal procedure.

Overall, the 5 studies included 1,918 participating patients who received at least one dose of patiomer. Of these, 64.6% suffered from chronic kidney disease with an eGFR of <6 mL/min/1.73 m², and 54.3% from diabetes mellitus and 77.9% from heart failure.

Study 1 (OPAL-HK)

Randomised, single-blind, two-part withdrawal study in patients with chronic renal insufficiency (CRI) and hyperkalaemia receiving stable doses of at least one RAAS inhibitor.

The safety and efficacy of Veltassa have been demonstrated in a randomised, single blind, two part withdrawal study evaluating Veltassa in patients presenting CRI and hyperkalaemia, receiving stable doses of at least one RAAS inhibitor (i.e. angiotensin converting enzyme

inhibitor [ACEI], angiotensin II receptor blocker [ARB] or [mineralocorticoid receptor antagonists](#) [MRA]).

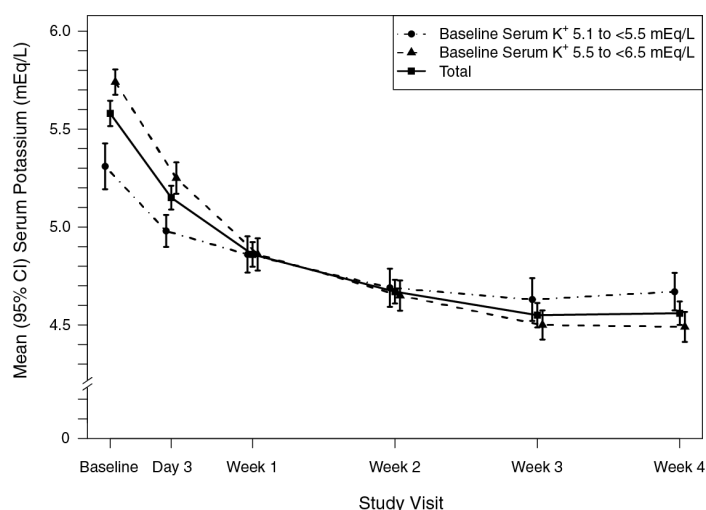
In part A, 243 patients were treated with Veltassa for 4 weeks. The initial dose of Veltassa was 8.4 g of patiromer daily (in fractionated doses) in patients with a potassium level from 5.1 mEq/L to <5.5 mEq/L (mmol/L) at baseline and 16.8 g of patiromer daily (in fractionated doses) in those with a potassium level from 5.5 mEq/L to <6.5 mEq/L at baseline. The dose was adjusted, as needed, on the basis of potassium level, determined starting from day 3 and then in bi-weekly visits (weeks 1, 2 and 3) to the end of the 4-week treatment period, for the purpose of maintaining potassium level within the target range (3.8 mEq/L to <5.1 mEq/L).

Mean patient age was 64 years, 58% of patients were male and 98% were of Caucasian origin. Approximately 97% of patients presented with hypertension, 57% with type 2 diabetes and 42% with heart failure.

Mean daily doses of Veltassa were 13 g and 21 g in patients with potassium levels of 5.1 to <5.5 mEq/L and 5.5 to <6.5 mEq/L, respectively.

Mean potassium level was 5.58 mEq/L at baseline and the mean variation (SD) of potassium level between the baseline visit and week 4 of part A was 1.01 (0.031) mEq/L, 95% CI: [-1.07; -0.95] (see figure 2). This mean reduction of potassium level was statistically significant. For the secondary endpoint of part A, 76% (95% CI: 70%, 81%) of patients had a potassium level in the target range of 3.8 mEq/L to <5.1 mEq/L at week 4 of part A.

Figure 2: Estimated mean (95% CI) potassium level (mEq/L) determined by the central laboratory over time



Baseline potassium level from 5.1 to <5.5 mEq/L
 Baseline potassium level from 5.5 to <6.5 mEq/L
 Total

Mean potassium level (95% CI) (mEq/L)

In Part B, 107 patients who had potassium levels from 5.5 mEq/L to <6.5 mEq/L at the baseline visit in part A, and whose potassium levels were within the target range (3.8 mEq/L to <5.1 mEq/L) at week 4 of part A and who were still receiving one or more RAAS inhibitors were randomised to continue treatment with Veltassa or to receive placebo for 8 weeks in order to evaluate the effect of discontinuing Veltassa on potassium levels. In the patients in the Veltassa group, the mean daily dose was 21 g at the start and during part B.

The primary endpoint in part B was the variation in potassium level from inclusion in part B until the first visit during which the patient's potassium level for the first time fell outside of the

range of 3.8 to <5.5 mEq/L or until week 4, if the patient's potassium level remained in this range. In part B, potassium levels increased by 0.72 mEq/L, 95%CI [0.46, 0.99] in patients receiving placebo, while showing no change in patients continuing treatment with Veltassa.

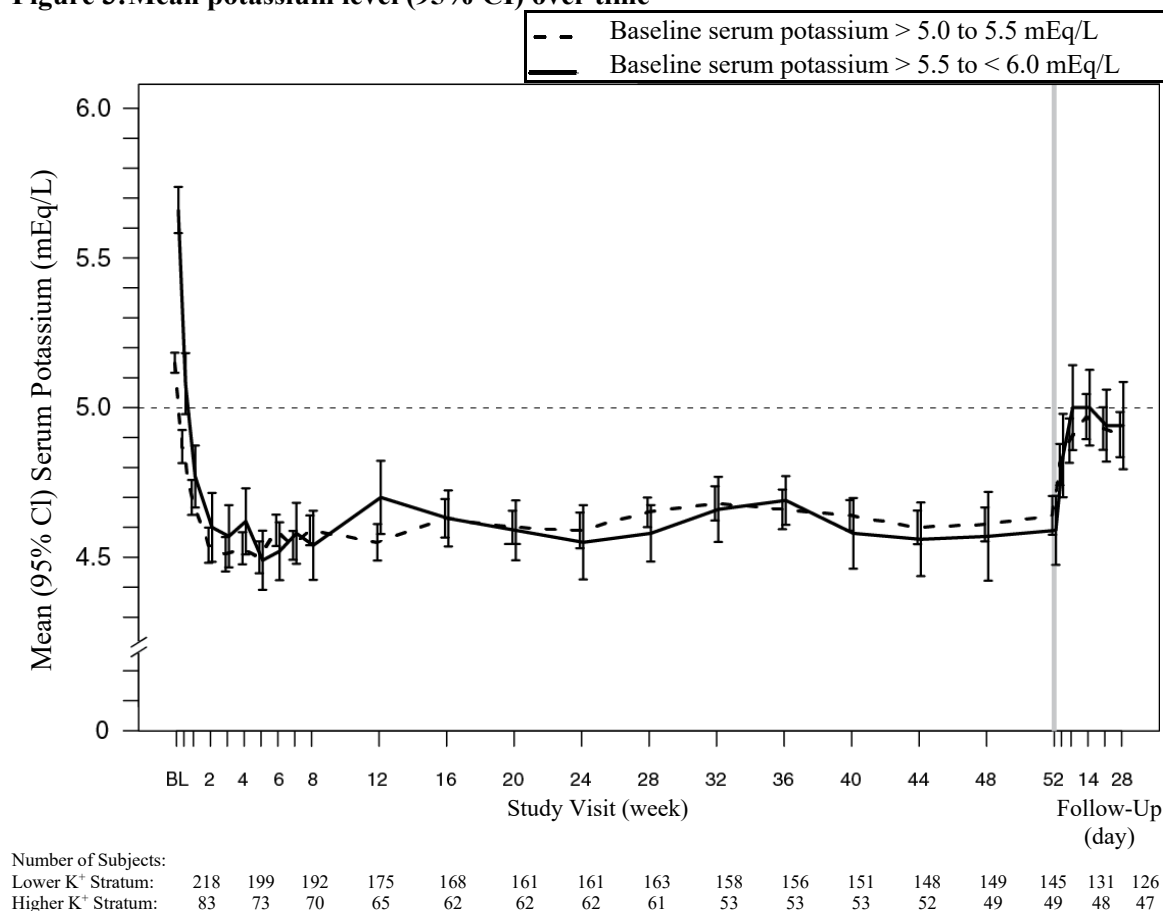
The percentage of patients having presented a serum potassium level ≥ 5.1 mEq/L at any point in part B was higher in the group receiving placebo (91% [95% CI: 83%, 99%]) than in the group treated with patiomer (43% [95% CI: 30%, 56%]). The percentage of patients having presented a potassium level ≥ 5.1 mEq/L at any point in part B was higher in the group receiving placebo (60% [95% CI: 47%, 74%]) than in the group treated with patiomer (15% [95% CI: 6%, 24%]).

Fifty two percent (52%) of patients receiving placebo needed to discontinue treatment with a RAAS inhibitor because of reoccurrence of hyperkalaemia *versus* 5% of patients treated with Veltassa.

Study 2 (AMETHYST-DN)

The effect of treatment with Veltassa for a duration of up to 52 weeks was evaluated in an open label study of 304 hyperkalaemic patients with CRI and type 2 diabetes on stable doses of a RAAS inhibitor. Reductions in potassium levels observed during treatment with Veltassa were maintained for one year with regular treatment. In patients with a baseline potassium level of >5.0 to 5.5 mEq/L having already received an initial dose of 8.4 g patiomer per day (in fractionated doses), the mean daily dose was 14 g. In those with a baseline potassium level of >5.5 to <6.0 mEq/L having already received an initial dose of 16.8 g patiomer per day (in fractionated doses), the mean daily dose was 20 g during the entire study.

Figure 3: Mean potassium level (95% CI) over time



Study 3 (PEARL-HF)

The ability of patiomer to enable concomitant spironolactone treatment was investigated in a randomised, double-blind, placebo-controlled study in heart failure patients who were

clinically indicated to receive MRA. Patients initiated spironolactone at 25 mg/day at the same time as their randomised treatment (patiromer 12.6 g BID or placebo), and were up-titrated to 50 mg/day after Day 14 if serum potassium was >3.5 and ≤ 5.1 mEq/L. Of the 105 patients who were randomised and received study treatment (patiromer 56; placebo 49), mean age was 68.3 years, 60.6% were men, 97.1% were Caucasian, and mean eGFR was 81.3 mL/min. Mean baseline serum potassium values were 4.71 mEq/L for patiromer and 4.68 mEq/L for placebo.

The primary efficacy endpoint, change from baseline in serum potassium to the end of the 28-day treatment period, was significantly lower ($p < 0.001$) in the patiromer group (LS mean [SEM]: -0.21 [0.07] mEq/L) as compared to the placebo group (LS mean [SEM]: $+0.23$ [0.07] mEq/L). There were also fewer patients in the patiromer group with serum potassium values >5.5 mEq/L (7.3% vs. 24.5%; $p = 0.027$) and more patients on spironolactone 50 mg/day (90.9% versus 73.5%, $p = 0.022$).

Study 4 (AMBER)

Another randomised, double-blind, placebo-controlled study investigated the effect of patiromer on the tolerability of spironolactone treatment in patients with treatment-resistant hypertension and CRI. During the study, patients were randomised to receive patiromer or placebo in addition to spironolactone (25 mg/day; increased to 50 mg/day from week 3 in patients with a systolic blood pressure ≥ 120 mmHg and a serum potassium of ≤ 5.1 mEq/L). To maintain a serum potassium level of between ≥ 4.0 mEq/L and ≤ 5.1 mEq/L, the patiromer/placebo dose could be increased on a weekly basis from the starting dose of 8.4 g/day to a maximum of 25.2 g/day.

A total of the 295 randomized patients (147 receiving patiromer; 148 receiving placebo) with a mean age of 68.1 years and a mean eGFR of 35.73 mL/min/1.73m² were randomised, stratified according to baseline serum potassium levels (mean serum potassium was 4.71 mEq/L in the patiromer arm and 4.68 mEq/L in the placebo control arm) and a history of diabetes mellitus (type 1 or type 2). The primary endpoint was the percentage of patients who continued spironolactone treatment until the end of the study (12 weeks). This percentage was significantly greater in the patiromer group than in the placebo group (85.7% versus 66.2%; $p < 0.0001$). Patients in the patiromer arm received a spironolactone dose of 50 mg/day more often (69.4% versus 51.4% in the placebo control arm) and their serum potassium levels were ≥ 5.5 mEq/L less often than patients in the placebo control arm (35.4% vs 64.2% in the placebo control; $p < 0.001$).

Study 5 (DIAMOND)

The effects of patiromer on serum potassium were examined in a double-blind, placebo-controlled, randomised-withdrawal, parallel-group study on patients who received the doses of RAASi inhibitors approved for the treatment of heart failure and maintained or achieved normokalaemia during the administration of patiromer. Before randomisation, the patients were either hyperkalaemic while they received RAASi inhibitors or normokalaemic with a history of hyperkalaemia during the intake of RAASi inhibitors in the preceding 12 months, which led to a decrease of the dose of RAASi inhibitors or to withdrawal from RAASi inhibitors. In all patients, patiromer was started at a dose of 8.4 g per day and titrated weekly up to a maximum dose of 25.2 g per day in order to maintain the serum potassium level of ≥ 4.0 mEq/L and ≤ 5.0 mEq/L. Hyperkalaemic patients received patiromer from the start; normokalaemic patients received patiromer in week 1 or later. In parallel to this, the medication with the RAASi inhibitor was optimised, including the start, dose escalation and maintenance of at least 50% of the prescribed ACEi/ARB/ARNI target doses and 100% of the prescribed MRA target doses. As soon as these RAASi inhibitor target doses were achieved and the patients showed stable serum potassium levels of ≥ 4.0 mEq/L and ≤ 5.0 mEq/L for at least one week, they were randomised to either patiromer or placebo.

Of the 1,168 patients in whom patiromer was started, 130 did not complete the run-in part. Of the 1,038 patients who did complete the run-in part, 878 (85%) were randomised (patiromer: 439, placebo: 439). The mean age of randomised patients was 66.9 years; 72.9% were men, 97.9% Caucasian, and the mean eGFR was 63.0 mL/min/1.73 m². At the time of randomisation, the mean baseline serum potassium value was 4.72 mEq/L.

All participants had a history of hyperkalaemia. At the start of the study, a total of 40.3% of the participants were hyperkalaemic and 59.7% were normokalaemic but had a history of hyperkalaemia in the preceding 12 months.

The primary efficacy endpoint was the difference between the adjusted mean change (standard error [SE]) of the serum potassium level from the baseline, which was analysed with a mixed model for repeated measures (MMRM). The difference of the adjusted mean changes compared to the baseline was 0.097 mEq/L (95% CI: -0.128; -0.067). The mean change in serum K⁺ from the baseline value was statistically significantly lower in the patiromer group (0.029 [0.019] mEq/L) (p 0.001) than in the placebo group (0.127 [0.019] mEq/L).

The time until the first hyperkalaemia event (defined as serum potassium level > 5.5 mEq/L) was significantly shorter for patiromer compared to placebo (p = 0.006), with a hazard ratio of 0.63 (95% CI: 0.45; 0.87).

The proportion of patients in whom the MRA medication (spironolactone or eplerenone) was reduced under the target dose was 13.9% in the patiromer group compared to 18.9% in the placebo group. The hazard ratio for the time until the first MRA dose reduction of patiromer compared to placebo was 0.62 (95% CI: 0.45; 0.87), and the treatment difference was statistically significant (p = 0.006).

In the pre-defined subgroups of eGFR $\leq$ 60 mL/min/1.73 m², $\leq$ 45 mL/min/1.73 m² with post-hoc analysis of eGFR $\leq$ 30 mL/min/1.73 m², patiromer allowed to use effective RAAS inhibitor doses, controlled serum K⁺ and minimised the risk of hyperkalaemia in patients with HFrEF and mild to severe chronic renal disease.

Overall, 31.2% of the patients in the patiromer group and 45.1% of the patients in the placebo group had at least one hyperkalaemia event with a serum potassium value of > 5.5 mEq/L reported by the investigator. The annualised event rate ratio for patiromer was 0.658 compared to placebo (95% CI: 0.534; 0.810), which was statistically significant (p < 0.001).

An unadjusted win-ratio approach was used for the two hierarchically tested secondary endpoints: one approach for which complex hyperkalaemia-dependent hard endpoints were used, including death from a cardiovascular cause, hospital stays due to cardiovascular diseases and three grades of hyperkalaemia events, showing a win ratio of 1.526 (95% CI: 1.231; 1.906; p < 0.001), which favours treatment with patiromer; and one in which a new score was used for the application of RAASi inhibitors (0–8 points), showing a good rate of achieving a high score for the application of RAASi inhibitors in patients treated with patiromer compared to the placebo group, with a win ratio of 1.4248 (95% CI: 1.003; 1.564; p = 0.048).

5.2 Pharmacokinetic properties

Absorption

Patiromer works by binding potassium in the gastrointestinal tract. Serum concentration is therefore not relevant for its efficacy. Because of the insolubility and non-absorption characteristics of Veltassa, many classic pharmacokinetic studies have not been possible to conduct.

In ADME (absorption, distribution, metabolism and excretion) studies with radiolabelling conducted in rats and dogs, patiromer was not systemically absorbed.

Distribution

Quantitative whole-body autoradiography analysis in rats demonstrated that radioactivity was limited to the gastrointestinal tract, with no detectable level of radioactivity in any other tissues or organs.

Biotransformation

Not applicable, because of Veltassa's insolubility and non-absorption characteristics.

Elimination

In ADME studies with radiolabelling in rats and dogs, patiromer was excreted through the faeces.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, toxicity to reproduction and development.

Patiromer did not demonstrate genotoxic effects in the reverse mutation studies (Ames test), chromosomal or micronucleus aberrations in rats.

No carcinogenicity studies have been conducted.

Patiromer had no negative impact on fertility in male or female rats at doses of up to 10 times the recommended maximum daily dose in humans (RMDH). Patiromer did not have any harmful effects on embryonic or foetal development, either, when administered to pregnant rats at doses of up to 6 g/kg, thus providing a margin of exposure 12 times greater than the RMDH and administered to pregnant rabbits at doses of up to 3 g/kg, thus providing a margin of exposure 6 times greater than the RMDH.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Xanthan gum

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

Veltassa may only be used up to the date marked with "EXP" on the packaging.

6.4 Special precautions for storage

Store and transport refrigerated (2°C – 8°C). Avoid any exposure to temperatures above 40°C.

Once issued to the patient, Veltassa can be kept at room temperature (below 25°C) for a maximum of 6 months.

Do not use Veltassa after the expiry date printed on the sachet.

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

Keep out of the sight and reach of children.

6.5 Nature and contents of container

8.4 g, 16.8 g of patiromer (as patiromer sorbitol calcium (patiromer sorbitex calcium)), as powder in sachets made of five layers: polyethylene, aluminium, polyethylene, polyester and paper.

Pack sizes: box of 30 sachets.

Not all strengths may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURER

Marketing Authorization Holder

Vifor Fresenius Medical Care Renal Pharma Ltd.
Rechenstrasse 37
9014 St. Gallen
Switzerland

Bulk manufacturing site

Corden Pharma Lisbon S.A.
R. da Indústria, 2
Quinta Grande
2610-088 Amadora
Portugal

Batch releasing site

Vifor (International) Inc.
Rechenstrasse 37
9014 St. Gallen
Switzerland

8. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 July 2017

9. DATE OF REVISION OF THE TEXT

May 2024