CSL Vifor

EU RISK MANAGEMENT PLAN FOR VELTASSA® (PATIROMER)

RMP version to be assessed as part of this application:

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Data Lock Point for this RMP:	1 August 2022
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LIST OF ABBREVIATIONS

ACEI	angiotensin converting enzyme inhibitor
AE	adverse event
ARB	angiotensin II receptor blocker
CKD	chronic kidney disease
ECG	electrocardiogram
EEA	European Economic Area
EU	European Union
GI	gastrointestinal
HF	heart failure
IV	intravenous
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
RAASi	renin angiotensin aldosterone system inhibitors
RLY5016	drug substance consisting of polymer anion (patiromer) with calcium as counterion
RLY5016S	drug substance consisting of polymer anion (patiromer) with a calcium-sorbitol counterion complex
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
SPS	sodium polystyrene sulfonate
UK	United Kingdom
US	United States

PART I: PRODUCT OVERVIEW

Active Substance(s) (INN or Common Name):	Patiromer (as patiromer sorbitex calcium)
Pharmaco-therapeutic Group(s) (ATC Code):	Drugs for treatment of hyperkalaemia and hyperphosphataemia, (V03AE09)
MAH or Applicant:	Vifor Fresenius Medical Care Renal Pharma France
Medicinal Products to Which this RMP Refers:	Veltassa 1 g/8.4 g/16.8 g/25.2 g powder for oral suspension
Invented Name(s) in the EEA:	Veltassa
Marketing Authorisation Procedure:	Centralised Procedure
Brief Description of the Product:	Chemical class: Veltassa is a highly cross-linked polymer of calcium 2-fluoroprop-2-enoate with diethenylbenzene and octa-1,7-diene, combination with D-glucitol (RLY5016S), belonging to the pharmacologic class of potassium binders. The drug substance consists of the polymer anion (the active moiety, patiromer) and a calcium-sorbitol counterion complex. This polymer is insoluble in aqueous and organic solvent systems. Summary of mode 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 GI tract. Binding of potassium reduces the concentration of free potassium in the GI lumen, resulting in a reduction of serum potassium levels.
Hyperlink to the Product Information:	See Section 1.3.1. Proposed: Product Information.
Indication(s) in the EEA:	Current: Veltassa is indicated for the treatment of hyperkalaemia in adults and adolescents aged 12 to 17 years.
Dosage in the EEA:	Current: The daily dose may be adjusted in intervals of 1 week or longer, based on the serum potassium level and the desired target range. Serum potassium should be monitored when clinically indicated. The duration of treatment should be individualised by the treating physician based on the need for serum potassium management. If serum potassium falls below the desired range, the dose should be reduced or discontinued. **Adults** The recommended starting dose is 8.4 g patiromer once daily. 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. **Adolescents Aged 12 to 17 Years** The recommended starting dose is 4 g patiromer once daily. Adjust the daily dose of patiromer based on the serum potassium level and the desired target range, up to a maximum dose of 25.2 g daily. It is recommended to switch to 8.4 g patiromer sachets if doses above 7 g are needed.

Pharmaceutical Form(s) and Strengths:	Current: Powder for oral suspension. Off-white to light-brown powder, with occasional white particles. Veltassa is supplied in single-use sachets. The sachets are available in 4 strengths: Each sachet contains 1 g patiromer (as patiromer sorbitex calcium). Each sachet contains 8.4 g patiromer (as patiromer sorbitex calcium). Each sachet contains 16.8 g patiromer (as patiromer sorbitex calcium). Each sachet contains 25.2 g patiromer (as patiromer sorbitex calcium).
Is/Will the Product be Subject to Additional Monitoring in the EU?	No

Notes: ATC=Anatomical Therapeutic Chemical; EEA=European Economic Area; GI=Gastrointestinal; INN=International Non-proprietary Name; MAH=Marketing Authorisation Holder; RMP=Risk Management Plan.

PART II: SAFETY SPECIFICATION

SI EPIDEMIOLOGY OF THE INDICATION AND TARGET POPULATION

SI.1 Epidemiology of the Disease

Indication

Veltassa is indicated for the treatment of hyperkalaemia (high potassium level in the blood) in adults and adolescents aged 12 to 17 years.

Hyperkalaemia is a condition that occurs when serum potassium levels are above the upper limit of normal which can vary across studies, however >5 mmol/l or 5 mEq/l is a common definition. In clinical studies supporting the indication of Veltassa for the treatment of hyperkalaemia, a serum potassium >5 mmol/l or mEq/l was used for entry.

Based upon 2022 population estimates, there are 447 million persons in the EU and 333 million in the US [1,2]. Using the estimated prevalence of 1.3%, the applicant estimates that 5.8 million patients will present with hyperkalaemia each year in the EU and 4.3 million in the US.

The presence of hyperkalaemia in patients with declining kidney function can range from 5% to 50% [3]. This condition can be dangerous and needs immediate medical attention to prevent possible complications.

The most common cause of high potassium is a failing kidney. When the kidney function is significantly reduced, the kidneys cannot remove extra potassium from the body and this could lead to potassium build-up. Other causes are certain drugs (e.g., angiotensin converting enzyme inhibitors (ACEIs), potassium-sparing diuretics, and other renin angiotensin aldosterone system inhibitors (RAASi)), burns, heart attack, heart failure (HF), dehydration, diabetes, and internal bleeding to name a few [4].

Too much potassium in the blood can cause problems with how nerves communicate with the muscles. This can lead to weakness or even paralysis. High potassium levels can also affect the heart and result in an abnormal heartbeat. This can be severe and can lead to death.

SI.1.1 Incidence and Prevalence

A recent pooled analysis of 542 articles used a random-effects model to estimate the incidence and prevalence of hyperkalaemia in the general population [5]. In this analysis, prevalence within the general population was reported to be 1.3% (1.0-1.8%) and the incidence was reported to be 0.4 (0.2-0.8) cases per 100 person-years.

Based upon 2022 population estimates, there are 447 million persons in the EU and 333 million in the US [1,2]. Using the estimated prevalence of 1.3%, it can be estimated

that 5.8 million patients will present with hyperkalaemia each year in the EU and 4.3 million in the US.

While rare in the general population of 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 [3,6].

SI.1.2 Demographics of the Target Population (Age, Sex, Race/Ethnic Origin)

Little evidence exists about the demographics of hyperkalaemia in the general population [7,8] and more is known about the profile of high risk patients, namely those patients with CKD and/or HF.

SI.1.3 Risk Factors for the Disease

The patients most at risk of hyperkalaemia are those with compromised renal excretion of potassium. Clinical risk factors for hyperkalaemia include CKD, diabetes mellitus, HF and older age [9,10] as well as the use of medications that reduce serum potassium excretion, notably RAASi such as ACEIs, angiotensin II receptor blockers (ARBs), aldosterone antagonists, angiotensin receptor neprilysin inhibitors and renin inhibitors [11-16]. Hyperkalaemia and/or the concern about the development of hyperkalaemia is a common reason that use of these drugs is limited in patients with CKD and/or HF where they have been shown to improve clinical outcomes [17-20]. 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 [14].

SI.1.4 Main Existing Treatment Options

A consensus paper supported by Kidney Disease: Improving Global Outcomes describes the treatment options for both acute and chronic hyperkalaemia [21].

In acute hyperkalaemia (serum potassium levels >6.0 mmol/l), the expert panel recommended treatment in a facility with cardiac monitoring, typically an emergency department [22].

Treatment includes intravenous (IV) calcium if electrocardiogram (ECG) changes are present or if the serum potassium is >6.5 mmol/l. IV insulin/glucose and/or salbutamol are recommended to shift potassium intracellularly. If acidosis is present without volume overload, sodium bicarbonate may be considered. These strategies either stabilise the cardiac membrane (calcium) or temporarily shift potassium into the cells to rapidly lower the serum potassium (insulin/beta adrenergic agonists and bicarbonate) [22].

Additional adjunctive therapies to treat hyperkalaemia, particularly those that enable potassium elimination in a relatively short amount of time, would provide another option for physicians when managing hyperkalaemia in acute settings. IV furosemide can be

considered unless the patient has severe volume depletion or is anuric. Potassium binders can also be considered to facilitate elimination of the potassium via the GI tract.

For patients in whom the aetiology of hyperkalaemia is not reversible but rather more chronic in nature from underlying CKD and/or use of RAASi, the traditional approach to management of hyperkalaemia 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 (SPS) (Resonium A®) and calcium polystyrene sulfonate (Calcium Resonium® 99.934% w/w powder for oral/rectal suspension) [23].

A new potassium binder was approved in the EU in March 2018 and US in May 2018; sodium zirconium cyclosilicate (Lokelma®) is insoluble, non-absorbed, formulated as a powder for oral suspension, and acts as a potassium-removing agent [24]. The most common adverse reaction with Lokelma was mild to moderate oedema. Each 5 g dose of Lokelma contains approximately 400 mg of sodium. In placebo-controlled trials up to 28 days, oedema was reported in 4.4%, 5.9%, 16.1% of patients treated with 5 g, 10 g and 15 g of Lokelma once daily, respectively versus 2.4% of patients receiving placebo. Because Lokelma can transiently increase gastric pH, there is the potential for drug-drug interaction. In general, oral medications with pH dependent solubility should be administered at least 2 hours before or 2 hours after Lokelma. Spacing is not needed if it has been determined the concomitant medication does not exhibit pH dependent solubility.

The use of dietary potassium restriction to manage hyperkalaemia is difficult due to the ubiquitous presence of potassium in foods. Because fat, carbohydrates (in diabetics), sodium and phosphorus tend to be restricted in patients with CKD, the addition of a potassium restriction severely limits food options, often resulting in noncompliance. Diuretics are a mainstay for managing sodium, water balance and hypertension, and are highly efficient at removing potassium in patients with normal renal function; however, the effectiveness of diuretics is greatly diminished in patients with CKD. Oral sodium bicarbonate does not reduce total body potassium, is not highly effective in reducing serum potassium levels and has not been well studied for the treatment of hyperkalaemia [25]. For patients who are receiving RAASi medications, clinical practice guidelines include the possibility of dose reduction or discontinuation of RAASi medication to address hyperkalaemia; however, this has the potential to attenuate the benefits of RAASi. The most recent guidelines note that, “the dose of ACEi or ARBs should only be reduced or discontinued as a last resort in patients with hyperkalaemia, after measures to control serum potassium have failed to achieve a normal serum potassium level” [21,26].

SPS is an ion-exchange resin that is indicated for the treatment of hyperkalaemia associated with anuria or severe oliguria or in patients requiring dialysis and in patients on regular haemodialysis or on prolonged peritoneal dialysis. SPS is not well tolerated, and its use can be associated with life-threatening side effects including intestinal necrosis. Further, an appreciable sodium load can occur with treatment such that caution is advised when SPS is administered to patients in whom an increase in sodium load may be detrimental

(e.g., congestive HF, hypertension, renal damage or oedema) [27]. The poor tolerability of repeated use of SPS and the risks associated with the product limit its utility in patients with CKD and HF, where the incidence of hyperkalaemia is highest [23,27,28]. Based on these factors, a recent retrospective cohort study utilising population-level databases from Manitoba, Canada reported low frequency of SPS prescription after an episode of hyperkalaemia (≥5.5 mmol/l) in adults with CKD and a RAASi prescription. RAASi discontinuation or down titration was the most common approach to manage hyperkalaemia [28].

SI.1.5 Natural History of the Indicated Condition in the Population, Including Mortality and Morbidity

Hyperkalaemia represents a serious condition that can result in life-threatening cardiac arrhythmias and is associated with an increased mortality risk [3] in patients with CKD. Severity of CKD and a history of hyperkalaemia have also been shown to be a multiplier of risk for sudden cardiac death [3]. These facts underscore the need to treat this clinical condition.

An elevation in the plasma (extracellular) potassium concentration decreases the ratio of intracellular to extracellular potassium, leading to partial depolarisation of the cell membrane. Hyperkalaemia accounts for considerable morbidity, e.g., it results in muscle weakness, paralysis, and arrhythmias such as ventricular extra systoles and fibrillation (ECG QRS widening), due to reduced myocardial conduction velocity. The effects on the conduction in the heart can become life-threatening and lead to sudden cardiac death. It is estimated that sudden cardiac death because of hyperkalaemia is the cause of death in 3-5% of dialysis patients [29].

In a retrospective analysis of the annualised mortality rate of a cohort of US patients using data from Truven Health Analytics MarketScan® Commercial and Medicare Supplemental Databases, populations of individuals with diagnoses of Type 2 diabetes mellitus and CKD Stage 3-5 during the 2009 baseline year was estimated (N=34,706). Mortality rates for the patient subpopulation meeting patiromer study enrolment criteria were estimated. The crude annualised mortality rate was 6.52 deaths per 100 patient-years. This was further analysed in a study population whose hyperkalaemia risk profile was similar to those patients enrolled in Study RLY5016-205 and the adjusted crude annualised mortality risk was 7.05% and rate was 7.30 deaths/100 patient-years. The observed annualised rate in Study RLY5016-205 was 5.70 deaths/100 patient-years when the rate was calculated based on the total duration of subject exposure in the study, which did not exceed that estimated from the corresponding matched Truven Health Analytics subpopulation [30].

SI.2 Important Comorbidities

Hyperkalaemia usually occurs in patients with compromised renal excretion of potassium arising from reduced renal filtration (i.e., reduced estimated glomerular filtration rate) and/or tubular defects.

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 dangerous levels. These acute clinical conditions require immediate treatment for hyperkalaemia, particularly when the degree of hyperkalaemia is severe (e.g., serum potassium ≥6.5 mEq/l) and/or associated with cardiac repolarisation disturbances. The risk of death is increased significantly in CKD patients with hyperkalaemia [3], underscoring the need to treat this clinical condition.

Overall, the comorbidities in the population studied are representative of the target patient population at risk for hyperkalaemia, including patients who are elderly (>65 years old), have advanced stages of CKD and HF, carry a high burden of associated cardiovascular and other comorbidities such as hypertension, diabetes, dyslipidaemia and ischaemic heart disease and are receiving typical concomitant medications expected for such a population including RAASi, beta blockers, digoxin, warfarin, diuretics, statins, hypoglycaemic agents and anti-platelet drugs [3].

SII NONCLINICAL PART OF THE SAFETY SPECIFICATION

SII.1 Toxicity

Key safety findings originating from this nonclinical development programme of Veltassa with the relevance to human usage are summarised below in Table 1.

Table 1 Key Nonclinical Safety Findings - Toxicity

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
Single-dose Toxicity	Data not available
Repeat-dose Toxicity	
4-week and 26-week oral toxicity studies in rats: No adverse clinical effects, and no toxicologically meaningful changes in clinical pathology (haematology, blood chemistry and urinalysis) or anatomic pathologic evaluations (gross pathology, organ weight and histopathology) were observed. The NOAELs for RLY5016 administered daily to rats in the diet for 4 weeks and for RLY5016S administered daily to rats in the diet for 26 weeks were >15 g/kg/day and >5 g/kg/day (expressed as RLY5016), respectively. No target organ toxicity was identified. 4-week and 39-week oral toxicity studies in dogs: No adverse clinical effects, and no toxicologically meaningful changes in clinical pathology (haematology, blood chemistry and urinalysis), anatomic pathologic evaluations (gross pathology, organ weight and histopathology), ophthalmic or ECG parameters were observed. Thus, the NOAEL for RLY5016 administered daily to dogs for 4 weeks was >7 g/kg/day; the NOAEL for RLY5016S administered daily to dogs for 39 weeks was determined to be 3.75 g/kg/day (expressed as RLY5016). No target organ toxicity was identified.	RLY5016 powder for oral suspension does not cause organ toxicity.
Reproductive/Developmental Toxicity	
Embryo/foetal development in rats: No RLY5016-related toxicity was observed in dams or litters of dams at oral doses up to 6 g/kg/day. Embryo/foetal development in rabbits: No RLY5016S-related toxicity was observed in dams or litters of dams at oral doses up to 3 g/kg/day (dose expressed in terms of RLY5016). Male and female fertility in rats: No RLY5016S-related toxicity was observed in male and female rats at oral doses up to 5 g/kg/day (dose expressed in terms of RLY5016).	RLY5016 powder for oral suspension has shown no evidence of embryonic/foetal toxicity, nor effects on reproductive function, development or fertility at dose levels up to 12-fold the MRHD (25.2 g/day). Animal reproduction studies are not always predictive of human response. RLY5016 powder for oral suspension is systemically not absorbed and has no systemic bioavailability and therefore is not expected to be excreted in human milk.

Table 1 Key Nonclinical Safety Findings - Toxicity (Cont'd)

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
Nephrotoxicity	
Repeat-dose toxicology studies (short-term and chronic studies in rats and dogs) results were consistent with the non-absorbed nature of the polymer and its lack of systemic bioavailability. No target organ toxicity was identified.	Repeat-dose toxicity studies demonstrated no target organ toxicity. Powder for oral suspension is systemically not absorbed, thus, there are no known or expected pharmacological effects on the organ system such as the liver or kidneys in humans.
Hepatotoxicity	
Repeat-dose toxicology studies (short-term and chronic studies in rats and dogs) results were consistent with the non-absorbed nature of the polymer and its lack of systemic bioavailability. No target organ toxicity was identified.	Repeat-dose toxicity studies demonstrated no target organ toxicity. RLY5016 powder for oral suspension is systemically not absorbed, thus, there are no known or expected pharmacological effects on the organ system such as the liver or kidneys in humans.
Genotoxicity	
Bacterial reverse mutation (Ames) assay: The bacterial reverse mutation assay was conducted with Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and Escherichia coli strain WP2uvrA in the absence and in the presence of metabolic activation. Concentrations of RLY5016 in the study ranged from 33.3–5,000 µg/plate. There were no test-article-induced increases in mutant frequency in any of the tester strains, either in the absence or in the presence of metabolic activation. In vitro mammalian chromosome aberration assay: The ability of RLY5016 to induce chromosome aberrations in Chinese hamster ovary cells was evaluated in the absence and presence of metabolic activation at concentrations of 15.6–500 µg/ml and 31.3-500 µg/ml, respectively. There were no test-article-induced increases in chromosome aberrations in the absence or presence of metabolic activation. In vivo micronucleus assay: Male rats were administered a single oral dose of RLY5016 at 0, 1, 3 or 6 g/kg. The frequency of micronucleated polychromatic erythrocytes in the bone marrow was assessed at 24 hours (all doses) and at 48 hours (high dose) after dosing. There were no test-article induced increases in the frequency of micronuclei in the bone marrow of RLY5016-treated rats; thus, RLY5016 was non-mutagenic in this assay.	RLY5016 powder for oral suspension does not show any metabolic activation in mutant frequency or chromosomal aberrations, as well as showing non-mutagenicity in the in vivo micronucleus assay, therefore, RLY5016 powder for oral suspension does not pose a genotoxic risk for humans.

Table 1 Key Nonclinical Safety Findings - Toxicity (Cont'd)

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
Carcinogenicity	Data not available. RLY5016S is not systemically absorbed and there have been no hyperplastic changes in animal studies of up to 39 weeks and no genotoxicity signal reported.

Notes: ECG=Electrocardiogram; MRHD=Maximum recommended human dose; NOAEL=No observed adverse effect level; RLY5016=Drug substance consisting of patiromer (polymer anion) with calcium as counterion; RLY5016S=Drug substance consisting of patiromer (polymer anion) with a calcium-sorbitol counterion complex.

The current nonclinical experience does not suggest areas of uncertainty or specific topics in need of further investigation.

SII.2 Safety Pharmacology as Applicable

General safety pharmacology findings from nonclinical studies are presented in Table 2 below.

Table 2 Key Nonclinical Safety Findings - General Safety Pharmacology

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
Cardiovascular System (Including Potential for QT Interval Prolongation)	
Cardiovascular assessment in dogs: Oral administration of RLY5016 at doses up to 3.5 g/kg in dogs produced no changes in cardiovascular parameters or ECG waveform measurements.	Given the nonclinical data, RLY5016 powder for oral suspension-related cardiovascular effects are not expected in humans.
Respiratory System	
Pulmonary assessment in anaesthetised rats: Oral administration of RLY5016 at doses up to 6 g/kg produced no significant respiratory changes in rats when compared with vehicle-treated animals.	Given the nonclinical data, RLY5016 powder for oral suspension-related respiratory effects are not expected in humans.
Central Nervous System	
Neuropharmacological profile in rats: Oral administration of RLY5016 at doses up to 6 g/kg in rats produced no changes in behavioural or physiological parameters.	Given the nonclinical data, RLY5016 powder for oral suspension-related neurobehavioural effects are not expected in humans.
Gastrointestinal System	
GI motility assessment in rats: There were no RLY5016-related changes observed on GI transit at 1 and 6 g/kg (oral gavage). However, administration of RLY5016 at 3 g/kg produced a slight, but statistically significant ($p<0.05$) decrease of 23% in GI transit compared with the vehicle group. Oral administration of RLY5016 at 1 g/kg produced no effect on stomach emptying when compared with the vehicle-treated group. However, RLY5016 administered at 3 and 6 g/kg produced a statistically significant ($p<0.01$) decrease in stomach emptying, as demonstrated by an increase in stomach weight (plus content) when compared with the vehicle group. Given the large doses of RLY5016 administered in this study (approximately 0.5 g in the 3 g/kg dose group and 1 g in the 6 g/kg dose group), residual RLY5016 in the stomach could be contributing to the significant increase (mean increase of 0.8 g) in the stomach weights (plus content) in these dose groups.	The effects noted on stomach emptying are considered to be physical, as opposed to pharmacological effects. The 3 and 6 g/kg doses used in this study are approximately 6- and 12-fold higher (on a weight basis) than the maximum daily dose of RLY5016 powder for oral suspension (25.2 g/day patiromer). Therefore, due to the large quantity of the RLY5016 administered to rats, this result is considered to not be reflective of similar response in humans.

Notes: ECG=Electrocardiogram; GI=Gastrointestinal; RLY5016=Drug substance consisting of patiromer (polymer anion) with calcium as counterion.

SII.3 Other Toxicity-related Information or Data as Applicable

No data regarding other toxicity findings were received from nonclinical studies.

Table 3 Other Toxicity-Related Information

Other Toxicity-Related Information	Relevance to Human Usage
Bioavailability	
Two single-dose studies, 1 in rats and 1 in dogs, were conducted to verify that the RLY5016 polymer anion is not systemically absorbed after oral administration. These studies used ^{14}C-labeled RLY5016 and demonstrated the non-absorbed nature of the polymer and its lack of systemic bioavailability.	RLY5016 powder for oral suspension is systemically not absorbed and has no systemic bioavailability. Quantitative whole-body autoradiography in rats did not detect any radiolabel outside the GI tract.
Drug-drug Interactions	
Binding of other orally administered drugs with RLY5016S was studied in vitro under conditions which mimic pH and cation conditions in different regions of the GI tract (pH 1.2, 4.5 and 6.8). Significant interaction (>30% binding) under at least 1 study condition was observed in vitro with RLY5016S and the following drugs: ciprofloxacin, trimethoprim, warfarin, cinacalcet, levothyroxine, clopidogrel, metformin, amlodipine, verapamil, lithium, quinidine, thiamine, quinapril, azilsartan, irbesartan, losartan potassium, olmesartan medoxomil, telmisartan, bisoprolol fumarate, carvedilol, metoprolol, nebivolol, finerenone, furosemide, torasemide and mycophenolate mofetil. To allow for a more realistic assessment of the DDI in the GI tract, a GI tract passage model was established and 7 drugs showing interaction with patiromer only at pH 1.2 were further tested in this model: quinapril, azilsartan, irbesartan, losartan potassium, olmesartan medoxomil, finerenone and torasemide. Adsorption to patiromer at pH 1.2 was reversible and declines as test drugs become neutral or negatively charged during GI tract passage. No interaction with patiromer with these 7 test drugs was observed in the GI tract model. No significant interaction under any study condition was observed in vitro with RLY5016S and the following drugs: acetylsalicylic acid, amoxicillin, cephalexin, apixaban, rivaroxaban, glipizide, allopurinol, atorvastatin, digoxin, phenytoin, riboflavin, benazepril, captopril, enalapril maleate, fosinopril, lisinopril, perindopril tert-butylamine, ramipril, trandolapril, candesartan cilexetil, valsartan, sacubitril, eplerenone, spironolactone, canagliflozin, dapagliflozin, empagliflozin, bumetanide, tacrolimus and sevelamer.	Since the patiromer polymer is not systemically absorbed, DDI, if they occur, would arise through binding of the polymer to another orally administered drug in the GI tract leading to a decrease in absorption of the other drug. The results of the in vitro DDI studies identified oral medications that have the potential to be bound by RLY5016 powder for oral suspension. The potential for DDIs was further evaluated in an extensive in vivo programme on healthy volunteers. As a precautionary measure, administration of patiromer should be separated by at least 3 hours from other oral medicinal products unless no interaction was confirmed in vivo.

Notes: DDI=Drug-drug interaction; GI=Gastrointestinal; RLY5016=Drug substance consisting of patiromer (polymer anion) with calcium as counterion; RLY5016S=Drug substance consisting of patiromer (polymer anion) with a calcium-sorbitol counterion complex.

SIII CLINICAL TRIAL EXPOSURE

During the clinical development of patiromer, 2 different drug substances (RLY5016S and RLY5016) were used to produce drug product for the clinical studies. RLY5016 refers to the polymer anion with calcium as counterion; RLY5016 contained the patiromer anion, which is the active moiety of RLY5016S. The clinical trial code RLY5016 was changed to patiromer after the submission and approval of Veltassa (patiromer) marketing authorisation. This change is reflected in this RMP.

SIII.1 Duration of Exposure

Safety data from 2,135 study participants who received at least 1 dose of patiromer in 10 clinical studies with patiromer in adults (Studies RLY5016-103, RLY5016-201, RLY5016-202, RLY5016-204, RLY5016-205, RLY5016-207, RLY5016-301, RLY5016-401, PAT-DEU-402, and PAT-CR-302) were pooled together and comprise the pooled safety population.

Safety data is available for 23 paediatric study participants, aged 6 to less than 18 years (Study RLY5016-206p (EMERALD)).

The exposure for adult and paediatric population is presented separately.

The following tables included in this section show exposure data by duration (Table 4 and Table 5), age and gender (Table 6 and Table 7), prescribed starting dose (Table 8 and Table 9), race (Table 10 and Table 11), and ethnicity (Table 12 and Table 13) from the completed clinical trials.

Table 4 Duration of Exposure to Patiromer in Adults (Pooled Safety Population)

Duration of Exposure	Safety Pooled Population (N=2,135)	
	Persons	Person-years
≥0 weeks (≥1 day)	2,135 (100.0%)	678.6
≥4 weeks (≥28 days)	1,607 (75.3%)	657.5
≥8 weeks (≥56 days)	1,026 (48.1%)	602.5
≥12 weeks (≥84 days)	726 (34.0%)	546.3
≥6 months (≥182 days)	477 (22.3%)	466.9
≥9 months (≥273 days)	377 (17.7%)	404.8
≥1 year (≥365 days)	239 (11.2%)	281.9
Total Person-years	**2,135 (100.0%)**	**678.6**

Notes: The pooled safety population includes participants treated with at least 1 dose of patiromer from 10 clinical studies (RLY5016-103, RLY5016-201, RLY5016-202, RLY5016-204, RLY5016-205, RLY5016-207, RLY5016-301, RLY5016-401, PAT-CR-302, and PAT-DEU-402).
Duration of exposure to study medication is calculated as the date of last dose of study medication - (date of first dose of study medication) + 1.
The date of last dose of study medication was identified by the Investigator. Duration of exposure may include days in which a 0 g/day patiromer dose was prescribed.
Person-years is calculated as the duration of exposure/365.25.
Source: Programme file: t_ex1.sas.

Table 5 Duration of Exposure to Patiromer in Paediatric Subjects (Study RLY5016-206p)

Duration of Exposure	6 to <12 Years Old (N=9)		12 to <18 Years Old (N=14)		Overall 6 to <18 Years Old (N=23)	
	Persons	Person-years	Persons	Person-years	Persons	Person-years
≥0 weeks (≥1 day)	9 (100.0%)	4.5	14 (100.0%)	6.6	23 (100.0%)	11.1
≥4 weeks (≥28 days)	9 (100.0%)	4.5	14 (100.0%)	6.6	23 (100.0%)	11.1
≥8 weeks (≥56 days)	9 (100.0%)	4.5	14 (100.0%)	6.6	23 (100.0%)	11.1
≥12 weeks (≥84 days)	9 (100.0%)	4.5	13 (92.9%)	6.4	22 (95.7%)	10.9
≥6 months (≥182 days)	5 (55.6%)	2.5	8 (57.1%)	4.1	13 (56.5%)	6.6
Total Person-years	**9 (100.0%)**	**4.5**	**14 (100.0%)**	**6.6**	**23 (100.0%)**	**11.1**

Notes: Duration of exposure to study medication is calculated as the date of last dose of study medication - (date of first dose of study medication) + 1.
The date of last dose of study medication was identified by the Investigator. Duration of exposure may include days in which a 0 g/day patiromer dose was prescribed.
Source: Programme file: t_ex2.sas.

Table 6 Exposure to Patiromer in Adults by Age and Gender (Pooled Safety Population)

Age	Male (N=1,426)		Female (N=709)		Safety Pooled Population (N=2,135)	
	Persons	Person-years	Persons	Person-years	Persons	Person-years
18 to <65 years	618 (43.3%)	209.1	210 (29.6%)	67.0	828 (38.8%)	276.1
≥65 years	808 (56.7%)	254.2	499 (70.4%)	148.3	1,307 (61.2%)	402.5
65 to <75 years	531 (37.2%)	171.0	276 (38.9%)	81.1	807 (37.8%)	252.2
75 to <85 years	248 (17.4%)	77.8	196 (27.6%)	62.1	444 (20.8%)	140.0
≥85 years	29 (2.0%)	5.4	27 (3.8%)	5.0	56 (2.6%)	10.4
Total Person-years	**1,426 (100.0%)**	**463.4**	**709 (100.0%)**	**215.3**	**2,135 (100.0%)**	**678.6**

Notes: The pooled safety population includes participants treated with at least 1 dose of patiromer from 10 clinical studies (RLY5016-103, RLY5016-201, RLY5016-202, RLY5016-204, RLY5016-205, RLY5016-207, RLY5016-301, RLY5016-401, PAT-CR-302, and PAT-DEU-402).
Person-years is calculated as the sum of person-years (duration of exposure/365.25).
Source: Programme file: t_ex_sex1.sas.

Table 7 Exposure to Patiromer in Paediatric Subjects by Age and Gender (Study RLY5016-206p)

Age	Male (N=14)		Female (N=9)		Overall (N=23)	
	Persons	Person-years	Persons	Person-years	Persons	Person-years
6 to <12 years	3 (21.4%)	1.5	6 (66.7%)	3.0	9 (39.1%)	4.5
12 to <18 years	11 (78.6%)	5.1	3 (33.3%)	1.5	14 (60.9%)	6.6
Total Person-years	**14 (100.0%)**	**6.6**	**9 (100.0%)**	**4.5**	**23 (100.0%)**	**11.1**

Notes: Person-years is calculated as the sum of person-years (duration of exposure/365.25).
Source: Programme file: t_ex_sex2.sas.

Table 8 Exposure to Patiromer in Adults by Prescribed Starting Dose (Safety Pooled Population)

Patiromer Starting Dose (g/day)	Safety Pooled Population (N=2,135)	
	Persons	Person-years
4.2	92 (4.3%)	8.3
5	6 (0.3%)	0.1
8.4	1,687 (79.0%)	484.8
10	63 (3.0%)	9.0
15	56 (2.6%)	3.9
16.8	100 (4.7%)	77.2
25.2	101 (4.7%)	76.4
33.6	30 (1.4%)	18.7
Total Person-years	**2,135 (100.0%)**	**678.6**

Notes: The pooled safety population includes participants treated with at least 1 dose of patiromer from 10 clinical studies (RLY5016-103, RLY5016-201, RLY5016-202, RLY5016-204, RLY5016-205, RLY5016-207, RLY5016-301, RLY5016-401, PAT-CR-302, and PAT-DEU-402).
Person-years is calculated as the sum of person-years (duration of exposure/365.25).
Source: Programme file: t_ex_dose1.sa.

Table 9 Exposure to Patiromer in Paediatric Subjects by Prescribed Starting Dose (Study RLY5016-206p)

Patiromer Starting Dose (g/day)	Overall (N=23)	
	Persons	Person-years
2	9 (39.1%)	4.5
4.2	14 (60.9%)	6.6
Total Person-years	**23 (100.0%)**	**11.1**

Notes: Person-years is calculated as the sum of person-years (duration of exposure/365.25).
Patiromer prescribed starting dose was 2 g/day and 4.2 g/day in subjects aged 6 to <12 and 12 to <18 years, respectively.
Source: Programme file: t_ex_dose2.sas.

Table 10 Exposure to Patiromer in Adults by Race (Safety Pooled Population)

	Safety Pooled Population (N=2,135)	
Race	Persons	Person-years
Caucasian descent	2,073 (97.1%)	671.5
Non-Caucasian descent	62 (2.9%)	7.2
Total Person-years	**2,135 (100.0%)**	**678.6**

Notes: The pooled safety population includes participants treated with at least 1 dose of patiromer from 10 clinical studies (RLY5016-103, RLY5016-201, RLY5016-202, RLY5016-204, RLY5016-205, RLY5016-207, RLY5016-301, RLY5016-401, PAT-CR-302, and PAT-DEU-402).
Person-years is calculated as the sum of person-years (duration of exposure/365.25).
Source: Programme file: t_ex_race1.sas.

Table 11 Exposure to Patiromer in Paediatric Subjects by Race (Study RLY5016-206p)

	6 to <12 Years Old (N=9)		12 to <18 Years Old (N=14)		Overall 6 to <18 Years Old (N=23)	
Race	**Persons**	**Person-years**	**Persons**	**Person-years**	**Persons**	**Person-years**
Caucasian descent	9 (100.0%)	4.5	14 (100.0%)	6.6	23 (100.0%)	11.1
Total Person-years	**9 (100.0%)**	**4.5**	**14 (100.0%)**	**6.6**	**23 (100.0%)**	**11.1**

Notes: Person-years is calculated as the sum of person-years (duration of exposure/365.25).
Source: Programme file: t_ex_race2.sas.

Table 12 Exposure to Patiromer in Adults by Ethnicity (Pooled Safety Population)

	Safety Pooled Population (N=2,135)	
Ethnicity	**Persons**	**Person-years**
Hispanic or Latino	230 (10.8%)	57.8
Not Hispanic or Latino	1,892 (88.6%)	619.1
Not reported	4 (0.2%)	1.1
Unknown	9 (0.4%)	0.6
Total Person-years	**2,135 (100.0%)**	**678.6**

Notes: The pooled safety population includes participants treated with at least 1 dose of patiromer from 10 clinical studies (RLY5016-103, RLY5016-201, RLY5016-202, RLY5016-204, RLY5016-205, RLY5016-207, RLY5016-301, RLY5016-401, PAT-CR-302, and PAT-DEU-402).
Person-years is calculated as the sum of person-years (duration of exposure/365.25).
Source: Programme file: t_ex_eth1.sas.

Table 13 Exposure to Patiromer in Paediatric Subjects by Ethnicity (Study RLY5016-206p)

	6 to <12 Years Old (N=9)		12 to <18 Years Old (N=14)		Overall 6 to <18 Years Old (N=23)	
Ethnicity	**Persons**	**Person-years**	**Persons**	**Person-years**	**Persons**	**Person-years**
Hispanic or Latino	0	0	1 (7.1%)	0.4	1 (4.3%)	0.4
Not Hispanic or Latino	9 (100.0%)	4.5	13 (92.9%)	6.2	22 (95.7%)	10.7
Total Person-years	**9 (100.0%)**	**4.5**	**14 (100.0%)**	**6.6**	**23 (100.0%)**	**11.1**

Notes: Person-years is calculated as the sum of person-years (duration of exposure/365.25).
Source: Programme file: t_ex_eth2.sas.

SIV POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Table 14 highlights the populations excluded from clinical trials with patiromer.

Table 14 Exclusion Criteria

Criterion	Reason for Exclusion	Considered to be Included as Missing Information?	Rationale
Known or suspected hypersensitivity to patiromer or any of its components.	Enrolling subjects with known hypersensitivity to constituents of Veltassa would place these patients at increased risk for additional hypersensitivity reactions.	No	If the patient is known to have a history of hypersensitivity reactions to the active substance or to any of the excipients, patiromer should not be given. This exclusion criterion will remain as a contraindication. Wording is included in SmPC Section 4.3 Contraindications.
Use in pregnant and lactating women.	Pregnant or lactating women were not enrolled in the clinical studies.	Yes	Animal reproductive and fertility studies at dose levels up to 6- and 12-fold, in rabbits and rats, respectively, revealed no evidence of impaired fertility or harm to the foetus, however, animal reproduction studies are not always predictive of human response. There are no data from the use of patiromer in pregnant women. Patiromer is not absorbed systemically following oral administration, and maternal use is not expected to result in foetal risk. Patiromer is not absorbed systemically by the mother, so breastfeeding is not expected to result in risk to the infant. This is addressed in the SmPC, Section 4.6 Fertility, pregnancy and lactation.
Use in patients with hepatic impairment.	These patients were excluded from the clinical trials.	No	This patient population was not the targeted population with hyperkalaemia but monitoring of hepatic enzymes was performed on all subjects in clinical trials regardless of their underlying comorbidities. No subject in the pooled studies permanently discontinued treatment with patiromer because of an AE related to an increase in hepatic enzymes or bilirubin. There are no known or expected pharmacological effects of this non-absorbed polymer on other organ systems such as the liver.

Table 14 Exclusion Criteria (Cont'd)

Criterion	Reason for Exclusion	Considered to be Included as Missing Information?	Rationale
Use in immunocompromised patients.	Patients included in the clinical trials must have a stable condition to accurately determine efficacy and safety in the clinical studies, and to ensure that ethical standards are met and to comply with the study protocol and procedure.	No	Immunocompromised patients should not be excluded from receiving treatment with patiromer if the benefit outweighs the risk, as determined by the prescribing physician.
Use in patients with a history of, or current diagnosis of a severe swallowing disorder, moderate to severe gastroparesis, GI motility disorders, bowel obstruction or severe GI disorders or major GI surgery (e.g., bariatric surgery or bowel resection).	The relevant site of action for patiromer is the lumen of the colon, where potassium is the most abundant cation due to active secretion and where the residence time of the polymer is the longest. This patient population was excluded in the clinical trials due to a potential class effect such as such as GI concretions, ischaemic colitis, GI tract ulceration or necrosis which could lead to intestinal perforations seen with other potassium binders and the mechanism of action of patiromer.	No	The GI-related AEs have been the most common AEs reported in clinical studies with patiromer, but they were mild to moderate in nature, self-limited, did not appear to be dose related, generally resolved spontaneously or with treatment, and none of them were reported as SAEs. The common GI AEs, occurring in ≥2% of subjects treated with patiromer included diarrhoea and constipation. They are considered as expected AEs due to the mechanism of action of patiromer [30]. The SmPC provides information under Section 4.4 Special warnings and precautions for use: GI Disorders: 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 patiromer should be carefully evaluated in adult and paediatric patients with current or history of severe gastrointestinal disorders, before and during the treatment.

Table 14 Exclusion Criteria (Cont'd)

Criterion	Reason for Exclusion	Considered to be Included as Missing Information?	Rationale
Use in patients with a history of alcohol/drug/chemical abuse within 1 year of screening.	Study specific exclusion criteria due to the risk for noncompliance in the use, storage, and handling of patiromer.	No	This exclusion criterion was not related to safety. These patients should not be excluded from receiving treatment with patiromer if the benefit outweighs the risk, as determined by the prescribing physician.
Use in patients with pseudo-hyperkalaemia due to haemolysis or to abnormally high numbers of platelets (>500,000/mm^3), leukocytes (>70,000/mm^3), or erythrocytes (haematocrit >55%) at screening based on the local laboratory results.	These patients will present with inaccurate baseline levels of potassium.	No	In clinical practice, the prescribing physician has the responsibility in deciding the appropriate treatment to be given to their patient considering the patient's underlying disease or other confounding factors.
Use in patients with heart or kidney transplant or anticipated need for transplant during study participation.	This patient population was excluded from clinical trials due to their underlying general health condition and to be able to determine the most reliable assessment of efficacy and safety.	No	In clinical practice, the prescribing physician will need to determine the appropriate treatment depending on which condition has greater importance.
Use in patients with symptoms associated with postural hypotension.	These patients were excluded to ensure the safety of the study population.	No	Patients with postural hypotension could worsen but can be monitored on symptomatology and can be managed by decreasing the dose of patiromer or discontinuing treatment if postural hypotension persists.

Table 14 Exclusion Criteria (Cont'd)

Criterion	Reason for Exclusion	Considered to be Included as Missing Information?	Rationale
Use in patients with any of the following cardio- or cerebrovascular events having occurred within 4 weeks prior to screening, including acute myocardial infarction, stroke (or transient ischaemic attack), a life-threatening atrial or ventricular arrhythmia, or resuscitated cardiac arrest.	Use in patients with any of the following cardio- or cerebrovascular events having occurred within 4 weeks prior to screening.	No	The patient population studied had many comorbidities such as CKD, HF, DM. Patients with hyperkalaemia should not be excluded from getting treatment with patiromer, regardless of underlying comorbidities, if the benefit outweighs the risk, as determined by the prescribing physician.
Use in patients treated with or who have taken potassium supplements, bicarbonate or baking soda in the last 7 days.	To accurately identify safety and efficacy of patiromer. Patients taking potassium supplements, bicarbonate or baking soda impacts the effectiveness measurement of treatment.	No	The prescribing physician has the responsibility to determine the best appropriate treatment for their patients and to take precaution in the possible interaction with other medications which have the same route and site of potassium absorption as patiromer. There may be a need for separation of dosing schedule of other medications.
Use in patients treated with or who have taken the following medications if doses have not been stable for at least 28 days prior to screening or if doses are anticipated to change during study participation: non-steroidal anti-inflammatory agents; COX-2 inhibitors; digoxin; bronchodilators; theophylline; heparins (including low molecular heparins).	Subjects included in the clinical studies must have a stable condition to accurately determine for efficacy and safety, including medications being taken for underlying conditions.	No	The prescribing physician has the responsibility to determine the best appropriate treatment for their patients and to take precaution in the possible interaction with other medications which have the same route and site of potassium absorption as patiromer. There may be a need for separation of dosing schedule of other medications.

Table 14 Exclusion Criteria (Cont'd)

Criterion	Reason for Exclusion	Considered to be Included as Missing Information?	Rationale
Use in patients with poorly controlled Type 1 or Type 2 diabetes mellitus, defined as recent adjustment in insulin prescription. Hospitalisation (either inpatient or emergency room treatment) for hyper- or hypoglycaemia.	Insulin reduces serum potassium by shifting it from extracellular fluid to intracellular fluid due to an increase in activity of the sodium-potassium pump, although temporarily and will affect the accurate level of serum potassium. The patient's condition on entering clinical studies had to be stable to be able to determine efficacy and safety accurately.	No	From the clinical studies, patiromer appears to be well tolerated for short and long periods (up to 1 year) of treatment in subjects with underlying CKD, DM and/or HF, a population with a high burden of comorbidities and high prevalence of hyperkalaemia [30]. Patients with hyperkalaemia should not be excluded from getting treatment with patiromer, regardless of underlying comorbidities, if the benefit outweighs the risk as determined by their treating physician.
Use in patients with active cancer, currently on cancer treatment or history of cancer in the past 2 years except for non-melanocytic skin cancer that is considered cured.	Subjects included in the clinical studies must have a stable condition to accurately determine for efficacy and safety, including medications being taken for underlying conditions.	No	Patients with hyperkalaemia should not be excluded from getting treatment with patiromer, regardless of underlying comorbidities, if the benefit outweighs the risk as determined by their treating physician.

Table 14 Exclusion Criteria (Cont'd)

Criterion	Reason for Exclusion	Considered to be Included as Missing Information?	Rationale
Serum magnesium <1.4 mg/dl (<0.58 mmol/l) at screening based on the local laboratory results.	Patiromer can encounter a series of distinct cation environments as it traverses the GI tract, marked by fluctuations in proton, sodium, potassium, calcium and magnesium concentrations.	No	Patients with magnesium level <1.4 mg/dl (<0.58 mmol/l) were excluded from the clinical studies due to the possibility of further lowering magnesium levels. The SmPC provides information under Section 4.4 Special warnings and precaution for use: Low Magnesium. In clinical trials, serum magnesium values <1.4 mg/dl (0.58 mmol/l) occurred in 9% of adult patients treated with patiromer. Mean decreases in serum magnesium were 0.17 mg/dl (0.070 mmol/l) or less. In a clinical trial involving paediatric patients, mean decrease in serum magnesium at Week 26 was 0.35 mg/dl (0.1440 mmol/l). No patients reached serum magnesium <1.4 mg/dl (0.58 mmol/l) during the paediatric clinical trial. Serum magnesium should be monitored for at least 1 month after initiating treatment and as clinically indicated during treatment, and magnesium supplementation considered in patients who develop low serum magnesium levels.

Table 14 Exclusion Criteria (Cont'd)

Criterion	Reason for Exclusion	Considered to be Included as Missing Information?	Rationale
Use in patients treated with or who have taken any one of the following medications (includes resins) 7 days prior to screening: sevelamer, calcium supplementation (acetate, carbonate, gluconate or other formulations), lanthanum carbonate, colesevelam, cholestyramine, colestipol, sodium or calcium polystyrene sulfonate, quinidine, drospirenone, tacrolimus, mycophenolate mofetil or cyclosporine.	Medications that may interfere with potassium binding activity of patiromer or may otherwise interact and must have a wash out period.	No	Patients with hyperkalaemia should not be excluded from getting treatment with patiromer, regardless of underlying comorbidities, if the benefit outweighs the risk as determined by their treating physician. The SmPC, Section 4.5, Interactions with other medicinal products and other forms of interaction, provides proposed recommendation for separating dosing of patiromer from other oral medicinal products by at least 3 hours.
Use in patients with BMI >40 kg/m^2.	Exclusion criteria in the studies to eliminate the subjects that may have uncontrolled insulin secretion or a possible defect in the sodium potassium-ATPase activity.	No	It is recommended not to take patiromer for oral suspension at the same time as drugs that have been shown to bind and other oral medications with a narrow therapeutic window that have not been tested. From the clinical studies, patiromer appeared to be well tolerated for short and long periods (up to 1 year) of treatment in subjects with underlying CKD, T2DM and/or HF, a population with a high burden of comorbidities and high prevalence of hyperkalaemia. The effect of BMI on efficacy or safety was not statistically or clinically significant.

Notes: AE=Adverse event; ATP=Adenosine 5'-triphosphatase; BMI=Body mass index; CKD=Chronic kidney disease; COX-2=Cyclooxygenase-2; DM=Diabetes mellitus; GI=Gastrointestinal; HF=Heart failure; PIP=Paediatric Investigational Plan; SAE=Serious adverse event; SmPC=Summary of Product Characteristics; T2DM=Type 2 diabetes mellitus.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

Table 15 Limitations to Adverse Drug Reaction Detection

Ability to Detect Adverse Reactions	Limitation of Trial Programme	Discussion of Implications for Target Population
Which are rare	To date, 2,135 adult subjects were exposed to patiromer within the clinical development programme for the proposed indication.	The exposure from the controlled randomised trials with patiromer may not be sufficient for capturing rare ADRs. Post-marketing surveillance will provide additional safety information on rare ADRs.
Due to prolonged exposure	Patiromer was studied for periods of up to 52 weeks in 2 studies: RLY5016-205 and PAT-CR-302. RLY5016-205, a 52-week Phase 2 trial, enrolled 306 subjects (of which 304 subjects received patiromer) with hyperkalaemia, CKD, hypertension, and Type 2 diabetes who were receiving ACEI and/or ARB medications with or without spironolactone. The study had 2 treatment periods: a treatment initiation period for 8 weeks, followed by a long maintenance period for an additional 44 weeks, which allowed treatment with patiromer for up to a total of 1 year.	The reported related AEs were mild to moderate in severity and resolved. The ability to detect ADRs which are due to prolonged exposure may have been affected by the duration of conducted clinical trials. Post-marketing surveillance will provide additional safety information regarding prolonged exposure.
Due to cumulative effects which have a long latency	Patiromer is non-absorbable and not systemically absorbed, thus limiting potential systemic toxicity and cumulative effects. Quantitative whole-body autoradiography in rats did not detect any radiolabel outside the GI tract. Distribution of the polymer is restricted to the GI tract; patiromer is expected to be excreted in faeces after approximately 24-48 hours, based on average GI transit time. The median duration of exposure in the patiromer safety population was 50 days overall (range: 1 to 796 days) [30]. Overall, 477/2,135 subjects (22.3%) received patiromer for at least 6 months, and 239/2,135 subjects (11.2%) received patiromer for at least 1 year. In the paediatric study, RLY5016-206p, all 23 subjects received patiromer for at least 8 weeks, and 22 (96%) and 13/23 (57%) of subjects received patiromer for at least 3 months and 6 months, respectively.	Data from the nonclinical and clinical studies showed no cumulative safety effects. All patients in the follow-up period had resolution of any TEAEs and did not report any recurrence within the end of the follow-up period. All related AEs resolved, even when patiromer was continued. Patiromer is non-absorbable and not systemically bioavailable. The occurrence of any safety concern with a long latency period is not expected for patiromer since it is not absorbed and not systemically available.

Notes: ACEI=Angiotensin converting enzyme inhibitors; ADR=Adverse drug reaction; AE=Adverse event; ARB=Angiotensin II receptor blocker; CKD=Chronic kidney disease; GI=Gastrointestinal; TEAE=Treatment-emergent adverse event.

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

Table 16 Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of Special Population	Exposure
Pregnant women Breastfeeding women	Not included in the clinical development programme.
Paediatric population age ≥6 to <18 years of age	The safety of patiromer in paediatric patients is under investigation. A PIP has been agreed with the Paediatric Committee of the EMA. The benefit/risk of patiromer in this population was investigated in the RLY5016-206p (EMERALD) study (23 patients aged ≥6 to <18 years). The safety and efficacy of patiromer for the treatment of hyperkalaemia was studied in patients 6 to less than 18 years of age. The safety profile of Veltassa in paediatric patients was generally comparable to that previously observed in adult patients. Most AEs that were reported as related, or possibly related, to patiromer were GI disorders in nature, including diarrhoea. No new risks or safety signals were identified with the use of patiromer in any age groups investigated in the trial. Patiromer has not been studied in paediatric patients below 6 years of age.
Elderly	From 2,135 subjects treated with patiromer in pooled clinical studies, 61% were age 65 years and over, and 23% were age 75 years and over. No overall differences in effectiveness were observed between these subjects and younger subjects, but subjects aged 65 years and older reported more GI and cardiovascular events than younger subjects [30]. However, interpretation of associations with age are confounded by potential differences in co-existing comorbidities or severity of comorbidities that are associated with older age in the population. No special dose and administration guidelines were applied to seniors in these studies.
Patients with Relevant Comorbidities:	
• Patients with severe hepatic impairment	Not included in the clinical development programme. The monitoring of the hepatic enzymes was performed on all subjects in clinical trials regardless of their underlying comorbidities. Patiromer is not systemically bioavailable, which is supported by the rat and dog repeat-dose toxicity studies which showed no organ toxicity.
• Patients with renal impairment	Hyperkalaemic patients often have CKD as a comorbidity. Of the 2,135 subjects in the pooled safety population, 64% had CKD at baseline, with a mean (SD) time since diagnosis of 3.9 (4.87) years. The most frequent CKD stages at baseline were CKD Stage 3b (36.0%), CKD Stage 3a (23.8%), and CKD Stage 4 (22.2%). No special dosing adjustments were needed for subjects with renal impairment.

Table 16 Exposure of Special Populations Included or Not in Clinical Trial Development Programmes (Cont'd)

Type of Special Population	Exposure
• Patients with cardiovascular impairment	A substantial proportion of the 2,135 subjects in the pooled safety population had cardiovascular disease at baseline, including 74% of subjects with HF and 36% of subjects with a history of MI. Furthermore, CKD, which increases risk for cardiovascular disease, cardiovascular death, and sudden cardiac death, was present at baseline in approximately 64% of subjects in the pooled safety population. Cardiovascular events were thus events of special interest in the clinical studies of patiromer, which were conducted primarily in subjects with significant cardiovascular comorbidities or risk factors [30]. Cardiac SAEs included cardiac failure (20/2,135 subjects, 0.9%), acute MI, cardiac failure acute, atrial fibrillation, and MI (0.2% each), angina unstable, ventricular tachycardia, acute left ventricular failure, acute coronary syndrome, cardiac failure chronic, coronary artery disease, and cardiorespiratory arrest (0.1% each). None of the cardiac-related SAEs were evaluated by the Investigator as related to patiromer. No cardiac AEs occurred in ≥2% of subjects treated with patiromer. The most common cardiac TEAEs, occurring in >0.5% of subjects, was cardiac failure (1.7% of subjects), atrial fibrillation (0.9% of subjects), and ventricular and supraventricular extrasystoles (0.7% of subjects, each).
Immunocompromised patients	Not included in the clinical development programme.
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development programme.
Population with relevant different ethnic origin	Not included in the clinical development programme.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development programme.

Notes: AE=Adverse event; CKD=Chronic kidney disease; GI=Gastrointestinal; HF=Heart failure; MI=Myocardial infarction; PIP=Paediatric Investigational Plan; SAE=Serious adverse event; SD=Standard deviation; TEAE=Treatment-emergent adverse event.

SV POST-AUTHORISATION EXPERIENCE

Veltassa was first authorised for marketing on 21 October 2015 in the US, where the product was launched in December 2015. The international birth date is commonly defined in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use E2C(R2) Periodic Benefit-Risk Evaluation Report Guideline as the date of the first marketing authorisation for the product granted to any company in any country in the world. For Veltassa, the international birth date is therefore defined as 21 October 2015.

On 19 July 2017, Veltassa has received marketing authorisation through the centralised procedure in the EU/EEA. To date, Veltassa is approved in 39 countries: EU/EEA (30 countries), US, Switzerland, UK, Australia, Canada, Israel, United Arab Emirates, Saudi Arabia, and Kuwait for the treatment of hyperkalaemia.

SV.1 Post-authorisation Exposure

SV.1.1 Method Used to Calculate Exposure

The exact number of patients exposed to Veltassa is not available. Assumptions considered to calculate patient exposure included obtaining the number of Veltassa boxes dispensed per month to patients in the 1 g, 8.4 g, 16.8 g and 25.2 g sachets. The number of patient-years has been calculated from the total amount of Veltassa powder for oral suspension (30 sachets in 1 carton) sold, assuming that a "standard patient" takes an average number of 1 sachet per day.

SV.1.2 Exposure

Worldwide cumulative patient exposure from post-marketing experience is presented in Table 17. From the international birth date up to the data lock point of this report, 40,227,728 sachets of Veltassa powder for oral suspension were commercially dispensed, corresponding to 111,744 patient-years.

Table 17 Cumulative Exposure from Marketing Experience Until 1 August 2022

Region	Exposure (Units)		No. of Cartons (1 Carton – 30 Sachets)
	Patient-years	Number of Sachets	
North America[1]	90,781	32,681,078	1,089,369
Latin America	0	0	0
Europe[2]	19,537	7,033,380	234,956
Africa	0	0	0
Middle East[3]	1,420	511,140	17,038
Asia Pacific[4]	6	2,130	71
Total	**111,744**	**40,227,728**	**1,341,434**

1 North America includes data from US and Canada.
2 Europe includes EU/European Economic area and Switzerland.
3 Middle East includes data from Saudi Arabia, UAE, Qatar, Israel and Kuwait.
4 Asia Pacific includes data from Australia.
Notes: Sales data is available on a monthly basis only, including data from the first to the last day of each month. Therefore, the cumulative exposure presented includes cumulative data from the international birth date up to 31 July 2022.

Details on age, gender or race/ethnic origin of exposed patients are not available. There are no specific data available on Veltassa use in special populations.

There are no signs of different patterns in Veltassa use other than in the authorised indication and target populations.

SVI ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATIONS

SVI.1 Potential for Misuse for Illegal Purposes

No potential or low potential, as it does not have systemic effects besides lowering potassium; narrow pharmacodynamic effects minimise the risk for illegal purposes.

Risk of drug abuse is low as Veltassa (patiromer) is subjected to medical prescription.

SVII IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

Not applicable, as this is not the first version of the RMP.

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

For the post-marketing safety database, a regular Medical Dictionary for Regulatory Activities version update is done.

Not applicable.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

SVII.2.1 Important Identified Risk Hypomagnesaemia/Low Magnesium

"Hypomagnesaemia/low magnesium" was maintained as an important identified risk as requested by the CHMP and the Pharmacovigilance Risk Assessment Committee (PRAC).

SVII.2.2 Important Potential Risk Increased Risk of Intestinal Perforation in Patients with Current or History of Severe GI Disorders is Removed from the List of Safety Concerns

"Increased risk of intestinal perforation in patients with current or history of severe GI disorders" was maintained as an important potential risk as requested by the CHMP and the PRAC.

SVII.2.3 Missing Information: Long-term Treatment in Patients <18 Years Old

Missing information: "long-term treatment in patients <18 years old" was included as a missing information as requested by the CHMP and the PRAC.

SVII.2.4 Missing Information: Treatment in Patients <6 Years Old

Missing information: "treatment in patients <6 years old" was removed from the list of safety concerns as requested by the CHMP and the PRAC.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Table 18 Important Identified Risk of Hypomagnesaemia/Low Magnesium

Identified Risk	Hypomagnesaemia/low magnesium
Frequency with 95% CI	**Clinical Trial Population** Frequency (%) N=2,135 (pooled safety population) Hypomagnesaemia: 65 (3.0%) lower limit (2.4%) upper limit (3.9%) Blood magnesium decreased: 11 (0.5%) lower limit (0.3%) upper limit (0.9%) Blood magnesium abnormal: Not reported 38 (1.8%) patients experienced an event of hypomagnesaemia, and 9 (0.4%) patients experienced an event of blood magnesium decreased, assessed as related to patiromer.
Seriousness/outcomes	No SAEs of hypomagnesaemia, blood magnesium decreased, and blood magnesium abnormal were reported. The majority of the reported hypomagnesaemia events resolved. No subjects in the pooled studies were permanently discontinued study drug or were considered as serious because of hypomagnesaemia or blood magnesium decreased.
Severity and nature of risk	Hypomagnesaemia was a common ADR seen in the clinical studies (1.8%). Subjects experienced a serum magnesium value of <1.4 mg/dl (7.1%), <1.2 mg/dl (1.8%), and <1.0 mg/dl (0.3%) at any time point in the clinical studies. No deaths or CV adverse events were attributable to low magnesium.
Background incidence/ prevalence	The incidence of hypomagnesaemia in the general population has been estimated at less than 2%. Some studies have estimated that 75% of Americans do not meet the recommended dietary allowance of magnesium [31]. In a Mayo Clinic review, magnesium levels of less than 1.7 mg/dl were noted in 13,320 of 65,974 hospitalised adult patients (20.2%). Hypomagnesaemia was common in patients with haematologic/oncological disorders [32]. The risk of hypomagnesaemia can be summarised as follows: • 2% in the general population • 10-20% in hospitalised patients • 50-60% in intensive care unit patients • 30-80% in persons with alcoholism • 25% in outpatients with diabetes
Risk groups or risk factors	The major risk factors for hypomagnesaemia in the population studied include a predominantly elderly population, CKD (Stage 2-4), diabetes, HF, hypertension, and prior myocardial infarction.
Potential mechanisms	The principal site of magnesium absorption is the proximal small intestine, with limited absorption in the ileum and colon. No extra-renal secretion mechanisms for magnesium excretion exist in the colon, thus RLY5016 powder for oral suspension binding in the colon is unlikely to significantly affect magnesium balance. Since the majority of magnesium uptake occurs in the small intestine, any remaining magnesium binding by RLY5016 powder for oral suspension in the colon would likely be minor.

Identified Risk	Hypomagnesaemia/low magnesium
Preventability	The applicant proposes to include in the SmPC under Section 4.4 Special warning and precautions for use: Low Magnesium In clinical trials, serum magnesium values <1.4 mg/dl (0.58 mmol/l) occurred in 9% of adult patients treated with patiromer. Mean decreases in serum magnesium were 0.17 mg/dl (0.070 mmol/l) or less. In a clinical trial involving paediatric patients, mean decrease in serum magnesium at Week 26 was 0.35 mg/dl (0.1440 mmol/l). No patients reached serum magnesium <1.4 mg/dl (0.58 mmol/l) during the paediatric clinical trial. Serum magnesium should be monitored for at least 1 month after initiating treatment and as clinically indicated during treatment, and magnesium supplementation considered in patients who develop low serum magnesium levels.
Impact on individual patient	All of the reported hypomagnesaemia events were mild to moderate, asymptomatic, and resolved in the majority of the cases. Unlikely to put patient at immediate risk, if magnesium levels are monitored in conjunction with potassium levels. Low magnesium level is easily reversible with magnesium supplements or fluids which contain electrolytes. Clinical symptoms of hypomagnesaemia, including neurologic and cardiac sequelae are generally not observed until serum magnesium levels are <1.0 mg/dl.
Potential public health impact of safety concern	There is no anticipated potential public health impact of this safety concern.
Evidence source	Clinical trial data: Summary of Clinical Safety Post-marketing safety data
MedDRA terms	MedDRA PTs: Hypomagnesaemia Blood magnesium decreased Blood magnesium abnormal

Notes: ADR=Adverse drug reaction; CI=Confidence interval; CKD=Chronic kidney disease; CV=Cardiovascular; HF=Heart failure; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred term; RLY5016=Drug substance consisting of patiromer (polymer anion) with calcium as counterion; SAE=Serious adverse event; SmPC=Summary of Product Characteristics.

Table 19 Important Potential Risk of Increased Risk in Patients with Current or History of Hypercalcaemia

Potential Risk	Increased Risk in Patients with Current or History of Hypercalcaemia
Frequency with 95% CI	**Clinical Trial Population** N=2,135 (pooled safety population) Frequency=6 (0.3%) Hypercalcaemia: 6 (0.3%) lower limit (0.1%) upper limit (0.6%). Blood calcium increased: Not reported. Blood calcium abnormal: Not reported. No subject in the safety population had an SAE related to abnormally high or low calcium, and no subject permanently discontinued treatment with patiromer because of a calcium-related AE. Serum calcium post-baseline data are available for 1,568 subjects treated with patiromer in the pooled safety population. Of these 1,568 subjects, 27 subjects (1.7%) had treatment-emergent serum calcium values >11 mg/dl (2.8 mmol/l). The highest serum calcium value recorded was 16.0 mg/dl.
Seriousness/outcomes	No SAEs of hypercalcaemia were reported.

Potential Risk	Increased Risk in Patients with Current or History of Hypercalcaemia
Severity and nature of risk	There were 6 reports of hypercalcaemia (mild) that occurred in patiromer clinical studies (pooled safety population).
Background incidence/ prevalence	Hypercalcaemia is a disorder that most commonly results from malignancy or primary hyperparathyroidism. The incidence of primary hyperparathyroidism alone is approximately 1-2 cases per 1,000 adults. Mild cases are often not diagnosed. A review of cancer-related hypercalcaemia found that rates varied by tumour type, being highest in multiple myeloma (7.5–10.2%) and lowest in prostate cancer (1.4–2.1%). Prevalence rates in large Scandinavian groups: as high as 39 cases per 1,000 persons. South Africa: 8 cases per 1,000 persons [33-36]. Hypercalcaemic crisis is a severe elevation of serum calcium, is usually considered as a value more than 14 mg/dl. Other, less common causes of elevated calcium include increased intake or absorption, granulomatous disease, immobilisation, thiazide diuretic use and familial hypocalciuric hypercalcaemia. In addition, a new trend in the diagnosis of CSS is based on the presence of hypercalcaemia with a normal parathyroid hormone level. The use of Vitamin D with calcium supplementation is known to contribute to the risk of hypercalcaemia in patients with CKD [37].
Risk groups or risk factors	Factors that increase the risk of hypercalcaemia: Malignancy, primary hyperthyroidism, calcium and Vitamin D supplements, antacids, granulomatous disease, immobilisation, thiazide diuretics, lithium, hyperthyroidism, and CKD especially advanced stage (end-stage renal disease). Risk groups: Scandinavian and South Africans.
Potential mechanism	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 GI tract. Binding of potassium reduces the concentration of free potassium in the GI lumen, resulting in a reduction of serum potassium levels. During cation exchange, a portion of the calcium in patiromer is released in the GI tract, some of which may be absorbed. Some of the released calcium is bound by luminal constituents (i.e., phosphate, oxalate) and becomes unavailable for absorption. These factors limit the risk of developing hypercalcaemia.
Preventability	The applicant proposes to include in the SmPC under Section 4.4 Special warnings and precautions for use: Information about calcium: 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 adult and paediatric patients at risk of hypercalcaemia. Serum calcium should be monitored for at least 1 month after initiating treatment and as clinically indicated during treatment.
Impact on benefit/risk balance of the product	There were 6 reported hypercalcaemia cases (mild) in patiromer in the clinical studies (pooled safety population). Total frequency of 0.05 per 100 patients (111,744 patient-years), case reports seen in post-marketing experience were mostly non-serious. Cases seen in post-marketing were also mild hypercalcaemia with some cases showing an unrelated causality. Unlikely to put patient at immediate risk, and the condition can be easily managed and reversible.
Potential public health impact of safety concern	There is no anticipated potential public health impact of this safety concern.
Evidence source and strength of evidence	Clinical trial data: Summary of Clinical Safety

Potential Risk	Increased Risk in Patients with Current or History of Hypercalcaemia
	Post-marketing safety data
MedDRA terms	MedDRA PTs: Hypercalcaemia Blood calcium increased Blood calcium abnormal

Notes: AE=Adverse event: CI=Confidence interval; CKD=Chronic kidney disease; CSS=Calcium supplement syndrome; GI=Gastrointestinal; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred term; SAE=Serious adverse event; SmPC=Summary of Product Characteristics.

Table 20 Important Potential Risk of Increased Risk of Intestinal Perforation in Patients with Current or History of Severe GI Disorders

Potential Risk	Increased risk of intestinal perforation in patients with current or history of severe GI disorders
Frequency with 95% CI	**Clinical Trial Population** Frequency (%) N=2,135 (pooled safety population) There were no reported cases of severe GI disorders such as GI ischaemia, necrosis and/or perforation that was considered as causally related to Veltassa in patiromer clinical studies (pooled safety population). The most common GI-related AEs (incidence ≥2%) included constipation, and diarrhoea.
Seriousness/outcomes	There were no reported GI-related AEs that were considered serious.
Severity and nature of risk	The majority of the GI AEs were mild to moderate in nature. GI AEs were severe in 0.5%. The potential for these mild to moderate GI AEs to aggravate a pre-existing condition such as haemorrhoids cannot be excluded and was not seen in the clinical studies.
Background incidence/ prevalence	All digestive diseases prevalence: 60 to 70 million people affected by all digestive diseases Ambulatory care visits: 48.3 million (2010) Hospitalisations: 21.7 million (2010) Mortality: 245,921 deaths (2009) Diagnostic and therapeutic inpatient procedures: 5.4 million—12 percent of all inpatient procedures (2007) Ambulatory surgical procedures: 20.4 million—20 percent of all “write-in” surgical procedures (2010) [38]
Risk groups or risk factors	Factors that increase the risk of death**:** Advanced age, presence of pre-existing underlying disease, malnutrition, the nature of the underlying or primary cause, and the appearance of complications [38].
Potential mechanisms	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.

Table 20 Important Potential Risk of Increased Risk of Intestinal Perforation in Patients with Current or History of Severe GI Disorders

Potential Risk	Increased risk of intestinal perforation in patients with current or history of severe GI disorders
Preventability	The applicant proposes to include in the SmPC under Section 4.4 Special warnings and precautions for use: Gastrointestinal Disorders 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 patiromer should be carefully evaluated in adult and paediatric patients with current or history of severe gastrointestinal disorders, before and during the treatment.
Impact on individual patient	All of the reported GI-related disorders were mild to moderate, self-limited and not dose dependent. Unlikely to put patient at immediate risk, if mild to moderate GI disorders are proactively managed to prevent the aggravation of a pre-existing condition. GI-related disorders are reversible with discontinuation of medication and/or treatment with laxatives.
Potential public health impact of safety concern	There is no anticipated potential public health impact of this safety concern.
Evidence source	Clinical trial data: Summary of Clinical Safety Post-marketing safety data
MedDRA terms	SOC Gastrointestinal Disorders

Notes: AE=Adverse event: CI=Confidence interval; GI=Gastrointestinal; MedDRA=Medical Dictionary for Regulatory Activities; SmPC=Summary of Product Characteristics; SOC=System organ class.

SVII.3.2 Presentation of the Missing Information

Table 21 Missing Information

Missing Information	What Is Known
Pregnancy or lactating women	
Evidence source:	<u>Anticipated risk/consequence of the missing information</u> Pregnancy: There are no data from the use of Veltassa in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see Section 5.3). As a precautionary measure, it is preferable to avoid the use of Veltassa during pregnancy. Breastfeeding: No effects on the breastfed newborn/infant are anticipated since the systemic exposure of the breastfeeding woman to patiromer 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. If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Use Veltassa during pregnancy only if your doctor considers it necessary.

Table 21 Missing Information

Missing Information	What Is Known
Long-term treatment in patients <18 years old	
Evidence source:	Population in need of further characterisation The long-term safety and efficacy of Veltassa in patients <18 years old have not yet been established. No data are available.

SVIII SUMMARY OF THE SAFETY CONCERNS

Table 22 Summary of Safety Concerns

Important identified risks	Hypomagnesaemia/low magnesium
Important potential risks	Increased risk in patients with current or history of hypercalcaemia
	Increased risk of intestinal perforation in patients with current or history of severe GI disorders
Missing information	Pregnant or lactating women
	Long-term treatment in patients <18 years old

Note: GI=Gastrointestinal.

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

All safety information will continue to be monitored in accordance with Good Pharmacovigilance Practices including regular review and evaluation of data. Routine pharmacovigilance entails evaluation and presentation of AEs in a Periodic Safety Update Report (PSUR), collecting data on AEs of concern.

Findings from routine pharmacovigilance will be communicated to the Agency through appropriate reports and the RMP will be updated upon newly detected findings.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

- Specific adverse reaction follow-up questionnaires for safety concerns

Not applicable.

- Other forms of routine pharmacovigilance activities for safety concerns

Not applicable.

III.2 Additional Pharmacovigilance Activities

Not applicable.

III.3 Summary Table of Additional Pharmacovigilance Activities

Not applicable.

Table 23 Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
N/A	N/A	N/A	N/A	N/A
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
N/A	N/A	N/A	N/A	N/A
Category 3 - Required additional pharmacovigilance activities				
N/A	N/A	N/A	N/A	N/A

Note: N/A=Not applicable.

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

No post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations are planned.

Table 24 Planned and Ongoing Post-authorisation Efficacy Studies That are Conditions of the Marketing Authorisation or That Are Specific Obligations

Study Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorisation				
N/A	N/A	N/A	N/A	N/A
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
N/A	N/A	N/A	N/A	N/A

Note: N/A=Not applicable.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

V.1 Routine Risk Minimisation Measures

The proposed routine risk minimisation measures are listed below. The effectiveness of the routine risk minimisation measures (such as SmPC, Patient Information Leaflet, pack size, legal status) will be regularly evaluated and assessed based on all received Individual Case Safety Reports from various sources following the pharmacovigilance processes in place. The outcome of these assessments will be summarised and discussed in the PSUR (including discussions about off-label use and medication errors) and will be reflected in the update of labelling documents and revisions of the RMP, as required and triggered by the signal detection and management, definition of new safety concerns and review of already identified and potential risks as well as missing information.

Currently, there are no additional risk minimisation measures in place or deemed necessary.

Table 25 Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Hypomagnesaemia/low magnesium	
Routine risk communication	SmPC Sections 4.4 and 4.8 PIL Section 2
Routine risk minimisation activities recommending specific clinical measures to address the risk	Recommendation to monitor serum magnesium at least 1 month after initiating Veltassa treatment, and to consider magnesium supplementation in patients who develop low serum magnesium levels.
Other routine risk minimisation measures beyond the Product Information	
Pack size	Veltassa 1 g is available in packs containing 60 sachets. Veltassa 8.4 g is available in packs containing 30, 60 or 90 sachets and multipacks comprising 3 cartons, each containing 30 sachets. Veltassa 16.8 g and 25.2 g are available in packs containing 30, 60 or 90 sachets.
Legal status	Prescription only medicine
Increased risk in patients with current or history of hypercalcaemia	
Routine risk communication	SmPC Section 4.4 PIL Section 2
Routine risk minimisation activities recommending specific clinical measures to address the risk	Recommendations to use Veltassa for patients at risk of hypercalcaemia following careful assessment of benefit/risk by the prescribing physician.

Table 25 Description of Routine Risk Minimisation Measures by Safety Concern (Cont'd)

Safety Concern	Routine Risk Minimisation Activities
Other routine risk minimisation measures beyond the Product Information	
Pack size	Veltassa 1 g is available in packs containing 60 sachets. Veltassa 8.4 g is available in packs containing 30, 60 or 90 sachets and multipacks comprising 3 cartons, each containing 30 sachets. Veltassa 16.8 g and 25.2 g are available in packs containing 30, 60 or 90 sachets.
Legal status	Prescription only medicine
Increased risk of intestinal perforation in patients with current or history of severe GI disorders	
Routine risk communication	SmPC Section 4.4 PIL Section 2
Routine risk minimisation activities recommending specific clinical measures to address the risk	Recommendation to carefully evaluate the benefit/risk of Veltassa in patients with current or history of severe gastrointestinal disorders, before and during treatment by the prescribing physician.
Other routine risk minimisation measures beyond the Product Information	
Pack size	Veltassa 1 g is available in packs containing 60 sachets. Veltassa 8.4 g is available in packs containing 30, 60 or 90 sachets and multipacks comprising 3 cartons, each containing 30 sachets. Veltassa 16.8 g and 25.2 g are available in packs containing 30, 60 or 90 sachets.
Legal status	Prescription only medicine
Use in pregnant and lactating women	
Routine risk communication	SmPC Section 4.6 PIL Section 2
Routine risk minimisation activities recommending specific clinical measures to address the risk	These special populations are highlighted in SmPC Section 4.6. There are no data from the use of patiromer in pregnant women; appropriate caution and benefit/risk assessment in treatment decision making by the prescribing physician are addressed in the aforementioned section.
Other routine risk minimisation measures beyond the Product Information	
Pack size	Veltassa 1 g is available in packs containing 60 sachets. Veltassa 8.4 g is available in packs containing 30, 60 or 90 sachets and multipacks comprising 3 cartons, each containing 30 sachets. Veltassa 16.8 g and 25.2 g are available in packs containing 30, 60 or 90 sachets.
Legal status	Prescription only medicine
Long-term treatment in patients <18 years old	
Routine risk communication	SmPC Section 4.2
Routine risk minimisation activities recommending specific clinical measures to address the risk	The data in adolescents aged 12 to 17 years are limited to 6 months exposure

Table 25 Description of Routine Risk Minimisation Measures by Safety Concern (Cont'd)

Safety Concern	Routine Risk Minimisation Activities
Other routine risk minimisation measures beyond the Product Information	
Pack size	Veltassa 1 g is available in packs containing 60 sachets. Veltassa 8.4 g is available in packs containing 30, 60 or 90 sachets and multipacks comprising 3 cartons, each containing 30 sachets. Veltassa 16.8 g and 25.2 g are available in packs containing 30, 60 or 90 sachets.
Legal status	Prescription only medicine

Notes: GI=Gastrointestinal; PIL=Patient Information Leaflet; SmPC=Summary of Product Characteristics.

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimisation Measures

Table 26 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Hypomagnesaemia/low magnesium	Routine risk minimisation measures: • SmPC Sections 4.4 and 4.8 • PIL Section 2 • Legal status: Prescription only medicine • Pack size: Veltassa 1 g is available in packs containing 60 sachets Veltassa 8.4 g is available in packs containing 30, 60 or 90 sachets and multipacks comprising 3 cartons, each containing 30 sachets Veltassa 16.8 g and 25.2 g are available in packs containing 30, 60 or 90 sachets Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Table 26 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern (Cont'd)

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Increased risk in patients with current or history of hypercalcaemia	Routine risk minimisation measures: • SmPC Section 4.4 • PIL Section 2 • Legal status: Prescription only medicine • Pack size: Veltassa 1 g is available in packs containing 60 sachets Veltassa 8.4 g is available in packs containing 30, 60 or 90 sachets and multipacks comprising 3 cartons, each containing 30 sachets Veltassa 16.8 g and 25.2 g are available in packs containing 30, 60 or 90 sachets Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Increased risk of intestinal perforation in patients with current or history of severe GI disorders	Routine risk minimisation measures: • SmPC Section 4.4 • PIL Section 2 • Legal status: Prescription only medicine • Pack size: Veltassa 1 g is available in packs containing 60 sachets Veltassa 8.4 g is available in packs containing 30, 60 or 90 sachets and multipacks comprising 3 cartons, each containing 30 sachets Veltassa 16.8 g and 25.2 g are available in packs containing 30, 60 or 90 sachets Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Use in pregnant and lactating women	Routine risk minimisation measures: • SmPC Section 4.6 • PIL Section 2 • Legal status: Prescription only medicine • Pack size: Veltassa 1 g is available in packs containing 60 sachets Veltassa 8.4 g is available in packs containing 30, 60 or 90 sachets and multipacks comprising 3 cartons, each containing 30 sachets Veltassa 16.8 g and 25.2 g are available in packs containing 30, 60 or 90 sachets Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Table 26 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern (Cont'd)

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Long-term treatment in patients <18 years old	Routine risk minimisation measures: • SmPC Section 4.2 • Legal status: Prescription only medicine • Pack size: Veltassa 1 g is available in packs containing 60 sachets Veltassa 8.4 g is available in packs containing 30, 60 or 90 sachets and multipacks comprising 3 cartons, each containing 30 sachets Veltassa 16.8 g and 25.2 g are available in packs containing 30, 60 or 90 sachets Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Notes: GI=Gastrointestinal; PIL=Patient Information Leaflet; SmPC=Summary of Product Characteristics.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for Veltassa (Patiromer)

This is a summary of the Risk Management Plan for Veltassa. The Risk Management Plan details important risks of Veltassa, how these risks can be minimised, and how more information will be obtained about Veltassa's risks and uncertainties (missing information).

Veltassa's Summary of Product Characteristics and its Package Leaflet give essential information to healthcare professionals and patients on how Veltassa should be used.

This summary of the Risk Management Plan for Veltassa should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report.

Important new concerns or changes to the current ones will be included in updates of Veltassa's Risk Management Plan.

I. The Medicine and What It Is Used for

Veltassa is authorised for the treatment of hyperkalaemia in adults and adolescents aged 12 to 17 years (see Summary of Product Characteristics for the full indication). It contains patiromer sorbitex calcium as the active substance and it is given orally.

Further information about the evaluation of Veltassa's benefits can be found in Veltassa's European Public Assessment Report, including in its plain-language summary, available on the EMA website, under the medicine's webpage (https://www.ema.europa.eu/en/medicines/human/EPAR/veltassa).

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Veltassa, together with measures to minimise such risks and the proposed studies for learning more about Veltassa risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the Package Leaflet and Summary of Product Characteristics addressed to patients and healthcare professionals.

- Important advice on the medicine's packaging.

- The authorised pack size - the amount of medicine in a pack is chosen so as to ensure that the medicine is used correctly.

- The medicine's legal status - the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Reports assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Veltassa is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Veltassa are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Veltassa. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	Hypomagnesaemia/low magnesium
Important potential risks	Increased risk in patients with current or history of hypercalcaemia
	Increased risk of intestinal perforation in patients with current or history of severe gastrointestinal disorders
Missing information	Pregnant or lactating women
	Long-term treatment in patients <18 years old

II.B Summary of Important Risks

Important identified risk	**Hypomagnesaemia/low magnesium**
Evidence for linking the risk to the medicine	Clinical trial data: Summary of Clinical Safety Post-marketing safety data
Risk factors and risk groups	The major risk factors for hypomagnesaemia in the population studied include a predominantly elderly population, CKD (Stage 2-4), diabetes, HF, hypertension, and prior myocardial infarction.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Sections 4.4 and 4.8 • PIL Section 2 • Legal status: Prescription only medicine • Pack size: Veltassa 1 g is available in packs containing 60 sachets Veltassa 8.4 g is available in packs containing 30, 60 or 90 sachets and multipacks comprising 3 cartons, each containing 30 sachets Veltassa 16.8 g and 25.2 g are available in packs containing 30, 60 or 90 sachets Additional risk minimisation measures: None
Important potential risk	**Increased risk in patients with current or history of hypercalcaemia**
Evidence for linking the risk to the medicine	Clinical trial data: Summary of Clinical Safety Post-marketing safety data
Risk factors and risk groups	Factors that increase the risk of hypercalcaemia: Malignancy, primary hyperthyroidism, calcium and Vitamin D supplements, antacids, granulomatous disease, immobilisation, thiazide diuretics, lithium, hyperthyroidism, and CKD especially advanced stage (end-stage renal disease). Risk groups: Scandinavian and South Africans.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4 • PIL Section 2 • Legal status: Prescription only medicine • Pack size: Veltassa 1 g is available in packs containing 60 sachets Veltassa 8.4 g is available in packs containing 30, 60 or 90 sachets and multipacks comprising 3 cartons, each containing 30 sachets Veltassa 16.8 g and 25.2 g are available in packs containing 30, 60 or 90 sachets Additional risk minimisation measures: None
Important potential risk	**Increased risk of intestinal perforation in patients with current or history of severe gastrointestinal disorders**
Evidence for linking the risk to the medicine	Clinical trial data: Summary of Clinical Safety Post-marketing safety data
Risk factors and risk groups	Factors increase the risk of death**:** Advanced age, presence of pre-existing underlying disease, malnutrition, the nature of the underlying or primary cause, and the appearance of complications [38].
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4 • PIL Section 2

	• Legal status: Prescription only medicine • Pack size: Veltassa 1 g is available in packs containing 60 sachets Veltassa 8.4 g is available in packs containing 30, 60 or 90 sachets and multipacks comprising 3 cartons, each containing 30 sachets Veltassa 16.8 g and 25.2 g are available in packs containing 30, 60 or 90 sachets Additional risk minimisation measures: None
Missing information	**Pregnant or lactating women**
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.6 • PIL Section 2 • Legal status: Prescription only medicine • Pack size: Veltassa 1 g is available in packs containing 60 sachets Veltassa 8.4 g is available in packs containing 30, 60 or 90 sachets and multipacks comprising 3 cartons, each containing 30 sachets Veltassa 16.8 g and 25.2 g are available in packs containing 30, 60 or 90 sachets Additional risk minimisation measures: None
Missing information	**Long-term treatment in patients <18 years old**
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.2 • Legal status: Prescription only medicine • Pack size: Veltassa 1 g is available in packs containing 60 sachets Veltassa 8.4 g is available in packs containing 30, 60 or 90 sachets and multipacks comprising 3 cartons, each containing 30 sachets Veltassa 16.8 g and 25.2 g are available in packs containing 30, 60 or 90 sachets Additional risk minimisation measures: None

Notes: CKD=Chronic kidney disease; HF=Heart failure; PIL=Patient Information Leaflet; SmPC=Summary of Product Characteristics.

II.C Post-authorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Veltassa.

II.C.2 Other Studies in Post-authorisation Development Plan

There are no other studies in post-authorisation development plan required for Veltassa.

A Paediatric Investigation Plan has been agreed by the Paediatric Committee of the EMA on 11 September 2015. This clinical study development plan for children includes studying RLY5016 powder for oral suspension in children and adolescents with hyperkalaemia from birth to 18 years of age. The proposed timeline for study start is in December 2016.

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