SUMMARY OF THE RISK MANAGEMENT PLAN (CH)
VELTASSA

Active Substance:	Patiromer (as patiromer sorbitex calcium) (chemical name: calcium, hydrolysed divinylbenzene-Me 2-fluoro-2-propenoate-1,7-octadiene polymer sorbitol complexes)
Anatomical Therapeutic Code:	V03AE09
MAH or Applicant:	Vifor Fresenius Medical Care Renal Pharma Ltd.
Medicinal Product(s) to Which this RMP Refers:	1
Products Concerned (Brand Names):	Veltassa 8.4 g powder for oral suspension Veltassa 16.8 g powder for oral suspension
Data Lock Point for this RMP:	20 July 2017
Date of Report:	9 February 2018
Version:	1.0

EXECUTIVE SUMMARY

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them. The RMP summary of Veltassa, powder for oral suspension is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the "Arzneimittelinformation/Information sur le médicament" approved and published in Switzerland, e.g., by mentioning risks occurring in populations or indications not included in the Swiss authorisation. Please note that the reference document which is valid and relevant for the effective and safe use of Veltassa, powder for oral suspension in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorised by Swissmedic. Vifor Fresenius Medical Care Renal Pharma Ltd. is fully responsible for the accuracy and correctness of the content of the published summary RMP of Veltassa, powder for oral suspension.

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LIST OF ABBREVIATIONS

CKD	Chronic kidney disease
EU	European Union
HF	Heart failure
RMP	Risk Management Plan
US	Unites States

VI.2 ELEMENTS FOR A PUBLIC SUMMARY

VI.2.1 Overview of Disease Epidemiology

Veltassa is used for the treatment of hyperkalaemia (high potassium level in the blood) in adults. Hyperkalaemia is a condition that occurs when your blood contains too much potassium. It is rare in the general population of healthy individuals with normal kidney function. The presence of hyperkalaemia in patients with declining kidney function can range from 5% to 50%. 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 your kidneys have significantly reduced function, they cannot remove extra potassium from the body and this could lead to potassium build-up. Other causes are certain drugs (e.g., loop diuretics, potassium-sparing diuretics, and thiazide diuretics), burns, heart attack, heart failure (HF), dehydration, diabetes, and internal bleeding to name a few.

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.

Based upon 2015 population estimates of 508 million persons in the EU and 320 million in the US, the Applicant estimates that 3.8 million patients will present with hyperkalaemia each year in the EU.

VI.2.2 Summary of Treatment Benefits

The safety and efficacy of Veltassa were demonstrated in clinical studies that evaluated Veltassa in patients with high potassium (hyperkalaemic patients) with chronic kidney disease (CKD) who were being treated with certain drugs (e.g., loop diuretics, potassium-sparing diuretics, thiazide diuretics). Studies were also done on patients with other kidney diseases caused by complications related to diabetes (also known as diabetic nephropathy) as well as in patients with heart disease.

Veltassa binds together with potassium, primarily in the large intestine, where excess potassium is most common. Then, both the potassium and Veltassa pass through and are removed from your body. Veltassa is not absorbed by your body.

Veltassa begins reducing levels of potassium within the first 4 hours after taking it and quickly removes excess potassium. Veltassa returns potassium levels to normal within 48 hours.

In 1 clinical study, 243 patients were treated with Veltassa for 4 weeks. Patients with a serum potassium of 5.1 mEq/l to <5.5 mEq/l received a starting Veltassa dose of 8.4 g patiromer per day and patients with a serum potassium of 5.5 mEq/l to <6.5 mEq/l received a starting Veltassa dose of 16.8 g patiromer per day. The dose of Veltassa was

increased or decreased as needed, based on the serum potassium level. The aim was to maintain serum potassium in the target range of 3.8 mEq/l to <5.1 mEq/l.

The mean age of patients in the study was 64 years; 58% of patients were men, and 98% were Caucasian. Approximately 97% of patients had hypertension, 57% had Type 2 diabetes, and 42% had HF.

At Week 4, the patients had a mean serum potassium decrease of -1.01 (0.031) mEq/l and 76% (95% confidence interval: 70%, 81%) of patients had a serum potassium in the target range of 3.8 mEq/l to <5.1 mEq/l.

In the second part of the study, 107 patients with a serum potassium of 5.5 mEq/l to <6.5 mEq/l and whose serum potassium was in the target range (3.8 mEq/l to <5.1 mEq/l) at Week 4 were to continue Veltassa or to receive placebo for 8 weeks to evaluate the effect of withdrawing Veltassa on serum potassium. The second part of the study showed that serum potassium rose by 0.72 mEq/l in patients on placebo relative to no change in patients who remained on Veltassa ($p<0.001$).

The effect of treatment with Veltassa for up to 52 weeks was evaluated in another study of 304 hyperkalaemic patients with CKD and Type 2 diabetes mellitus. Decreases in serum potassium with Veltassa treatment were maintained over 1 year of chronic treatment with a low incidence of hypokalaemia and the majority of subjects reaching and maintaining target serum potassium levels.

The common (may affect 1 in 10 people) side effects seen in the studies were constipation, diarrhoea, abdominal pain, wind, and low blood magnesium. The uncommon (may affect up to 1 in 100 people) side effects were nausea and vomiting. All of these side effects were mild to moderate in nature.

VI.2.3 Unknowns Relating to Treatment Benefits

Children and adolescents: The safety and efficacy of RLY5016 powder for oral suspension (Veltassa) has not been established.

Pregnancy and lactation: The safety and efficacy of RLY5016 powder for oral suspension (Veltassa) has not been studied in pregnant women or lactating mothers.

Drug-drug interactions with medications not studied: An extensive in vitro and in vivo program was conducted, and has shown that for all tested drugs a 3 hour separation with Veltassa prevents significant interaction. However these studies could not include all possible drugs.

VI.2.4 Summary of Safety Concerns

Table 1 Important Identified Risks

Risk	What is Known	Preventability
Low magnesium level (hypomagnesaemia)	Hypomagnesaemia was a common ADR seen in clinical studies (mild to moderate), although no subject experienced a value <1.4 mg/dl and none of the subjects reported SAEs of hypomagnesaemia. No subjects were discontinued due to hypomagnesaemia. Low baseline serum magnesium levels were present in about 10% (magnesium <1.8 mg/dl) and <1% (<1.4 mg/dl) of patients. These baseline deficiencies in magnesium may be related to coinciding nutritional deficiencies in a predominantly elderly population that was studied and/or result of concomitant use of magnesium wasting loop or thiazide diuretics which were prescribed in over 50% of the safety population at baseline. Further the magnesium lowering appears to be reversible when study drug was stopped and can be managed with magnesium supplementation.	In the Swiss Product Information under Section 7 Special warnings and precaution for use: Hypomagnesaemia Patiromer may cause hypomagnesaemia by binding magnesium in the colon. In clinical studies, magnesium levels <1.4 mg/dl were observed in 9% of patients treated with Veltassa, with no patients developing magnesium levels <1.0 mg/dl. Mean reductions in magnesium level occurred at the start of treatment with Veltassa and were ≤0.17 mg/dl throughout the entire course of treatment. Magnesium levels must be monitored for 1 month after initiating treatment with Veltassa and monitoring should be continued in the event of decreased serum levels of magnesium. Magnesium supplementation should be planned in patients who develop hypomagnesaemia during treatment with Veltassa.

Notes: ADR=Adverse drug reaction; SAE=Serious adverse event.

Table 2 Important Potential Risks

Risk	What is Known	Preventability
Increased risk of intestinal perforation in patients with current or history of severe GI disorders	The GI-related AEs have been the most common AEs reported in clinical studies with RLY5016 powder for oral suspension (Veltassa), 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 most common GI-related AEs (incidence ≥2%) included constipation, diarrhoea, nausea, abdominal discomfort and flatulence and are considered as expected AEs due to the mechanism of action of RLY5016 powder for oral suspension. Patients with a history of bowel obstruction or major GI surgery, severe GI disorders, or swallowing disorders were not included in the clinical studies.	In the Swiss Product Information under Section 7 Special warnings and precautions for use: Gastrointestinal disorders Patients with a history of intestinal blockage or major digestive surgery, diabetic gastroparesis, presenting severe gastrointestinal disorders or swallowing disorders were not included in the clinical studies. Treatment with Veltassa should be avoided in these patients.
Increased risk in patients with current or history of hypercalcaemia	There was a single (mild) AE of hypercalcaemia and this was reported to be unrelated to RLY5016 powder for oral suspension and resolved spontaneously. Did not necessitate withdrawal from study treatment (RLY5016-205 CSR Section 12.4.2.4 and Section 12.2.3.4.2).	In the Swiss Product Information under Section 7 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. However, in clinical studies with durations up to 1 year, no meaningful changes in mean serum calcium levels were observed. The benefits and risks of administering this medicinal product should be carefully evaluated by the physician in at-risk patients.

Notes: AE=Adverse event; GI=Gastrointestinal, SAE=Serious adverse event.

Table 3 Missing Information

Risk	What is Known
Pregnant and lactating patients	The safety and efficacy of RLY5016 powder for oral suspension (Veltassa) has not been studied in pregnant women or lactating mothers. No patients became pregnant or were lactating during the clinical trials.
Treatment in patients <18 years of age	The safety and efficacy of RLY5016 powder for oral suspension (Veltassa) in patients <18 years of age has not been established. The safety profile for this patient population is unknown.
Drug-drug interactions with medications not studied	The safety and efficacy of RLY5016 powder for oral suspension (Veltassa) in patient that may have a possible drug-drug interaction on other oral medications not studied with a 3 hours separation.

VI.2.5 Summary of Risk Minimisation Measures by Safety Concern

All medicines have a product information which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, the risks and recommendations for minimising them. The measures in these documents are known as routine risk minimisation measures.

The Swiss Product Information for RLY5016 powder for oral suspension (Veltassa) can be found at www.swissmedicinfo.ch.

RLY5016 powder for oral suspension (Veltassa) has no additional risk minimisation measures.

VI.2.6 Planned Post-authorisation Development Plan

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.

VI.2.7 Studies Which Are a Condition of the Marketing Authorisation

There are currently no post-authorisation efficacy studies for RLY5016 powder for oral suspension that have specific obligations and/or conditions of the marketing authorisation to date.

VI.2.8 Summary of Changes to the RMP Over Time

Not applicable.