

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205739Orig1s000**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Final Risk Evaluation and Mitigation Strategy (REMS) Review**

Date: October 21, 2015

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Drug Name(s): Veltassa<sup>TM</sup> (patiomer)

Therapeutic Class: Potassium binder

Dosage and Route: 8.4 g, 16.8 g and 25.2 g patiomer/packet

Application Type/Number: NDA 205739

Applicant/sponsor: (b) (4)

OSE RCM #: 2014-2294

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## 1 INTRODUCTION

The purpose of this review is to document the Division of Risk Management's (DRISK) evaluation of the need for a risk evaluation and mitigation strategy (REMS) for Veltassa™ (patiomer). Patiomer is a new molecular entity (NME), NDA 205739, submitted by Relypsa, Inc. (Relypsa) for the treatment of hyperkalemia. The initial NDA was received October 21, 2014 and was accepted for filing on December 20, 2014. There was no proposed risk management plan submitted with this application.

### 1.1 PRODUCT BACKGROUND

Patiomer is a non-absorbed, cation-exchange polymer with the proposed indication for treatment of hyperkalemia. Patiomer increases fecal potassium excretion through binding of potassium in the lumen of the gastrointestinal (GI) tract. Binding of potassium reduces the concentration of free potassium in the GI lumen, resulting in a reduction of serum potassium levels. Distribution is restricted to the GI tract and is expected to be excreted after approximately 24-48 hours (based on average GI transit time). Patiomer is not systemically bioavailable and is excreted in the feces. The site of action is the lumen of the colon where, due to active secretion, potassium is the most abundant cation, and where the residence time of the polymer is the longest.

The drug is likely to be dispensed to both inpatients and outpatients and likely to be prescribed by general practitioners and specialists. Patiomer is an oral suspension given once daily with food. It is supplied in single-use packets to be mixed with water. At the present time, the Applicant is proposing three packet strengths containing 8.4 grams, (b) (4) grams or 25.2 grams patiomer. The recommended starting dose of Veltassa is 8.4 grams patiomer once daily. Prescribers should monitor serum potassium and adjust the daily dose of Veltassa based on the serum potassium level and the desired target range. The dose may be increased or decreased by 8.4 grams daily, as necessary, to reach the desired range, up to a maximum dose of 25.2 grams once daily. The dose can be up-titrated based on serum potassium level at 1-week or longer intervals.

### 1.2 DISEASE BACKGROUND

Hyperkalemia is defined as serum potassium concentrations  $>5.5\text{mEq/L}$  due to either excess total body stores or abnormal movement of potassium out of the cells. Contributing factors include increased dietary intake, medications that impair renal excretion, metabolic acidosis and acute or chronic kidney disease (CKD). Clinical manifestations include muscle weakness or paralysis, cardiac conduction abnormalities, and cardiac arrhythmias. If left untreated, hyperkalemia can lead to impaired nerve function, arrhythmias and cardiac arrest. Treatment depends on both the degree of hyperkalemia and severity of clinical manifestations and includes either removal of excess potassium from the body (cation-exchange resins, hemodialysis), or shifting potassium into cells (beta-adrenergic agonists, diuretics and insulin with dextrose). In patients with hypertension without risk factors for hyperkalemia, the incidence of hyperkalemia with RAAS inhibitor monotherapy is low ( $<$  or  $=2\%$ ), whereas rates are

higher with dual RAAS inhibition (approximately 5%). The incidence of hyperkalemia is also increased in patients with heart failure or CKD (5% to 10%)<sup>1</sup>.

To date, sodium polystyrene sulfonate (SPS), marketed under the tradename Kayexalate<sup>®</sup>, is the only cation-exchange resin approved in the U.S. for the treatment of hyperkalemia. SPS was approved for treatment of hyperkalemia in June 1958, prior to the 1962 amendments to the Federal Food, Drug, and Cosmetic Act which required drug manufacturers to prove scientifically that a medication was not only safe, but effective. It is available as a suspension which can be administered orally or rectally and is dosed between one and four times a day, as needed.

### 1.3 REGULATORY HISTORY

The following is a summary of the regulatory history relevant to DRISK's evaluation of the need for a REMS for Veltassa:

**October 21, 2014:** Relypsa submitted NDA 205739 for Veltassa. The submission did not include a proposed REMS or risk management plan.

**April 2, 2015:** Mid-Cycle teleconference communication with Applicant, in which the Agency recommended once daily dosing due to the possibility of drug-drug interactions. In addition, the Agency indicated that they were considering a boxed warning and Medication Guide (MG) (outside of a REMS) to address this risk.

**May 20, 2015:** Applicant submitted an amendment to NDA 205739 that included draft labeling, MG, and Instructions for Use (IFU)

**August 7, 2015:** Division of Cardiovascular and Renal Products/DRISK met to discuss the potential mechanisms to mitigate the risk of a drug-drug-interaction and concluded that a REMS would not be required to mitigate this risk at this time.

## 2 MATERIALS REVIEWED

The following materials were used to inform the review:

- Relypsa, Inc. Summary of Clinical Efficacy for Veltassa (patiromer), received October 21, 2014
- Relypsa, Inc. Summary of Clinical Safety for Veltassa (patiromer), received October 21, 2014
- Relypsa, Inc. Draft Prescribing Information for Veltassa (patiromer), received October 21, 2014
- Relypsa, Inc. Amendment to Submission: Response to Information Request (Sequence No. 0012), received May 28, 2015
- Xiao, S. Medical Officer Review for Veltassa (patiromer), dated June 19, 2015
- Lai, J. Clinical Pharmacology Review for Veltassa (patiromer), dated October 12, 2015

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<sup>1</sup> [Clin J Am Soc Nephrol](#). 2010 Mar;5(3):531-48. doi: 10.2215/CJN.07821109. Epub 2010 Feb 11.

- Southworth, M. TSI 1510-Sodium Polystyrene Sulfonate (Kayexalate-NDA 11-287) and drug interactions Memo, Dated August 24, 2015

### **3 OVERVIEW OF CLINICAL PROGRAM**

The clinical development program for patiomer is comprised of eight studies- three Phase 1 studies, four Phase 2 studies and one two-part Phase 3 study (RLY5016-301). A total of 791 subjects participated in these clinical studies, including patients with hyperkalemia, CKD, heart failure, diabetes, hypertension and/or patients who were receiving dialysis and healthy volunteer subjects; 734 subjects received at least one dose of RLY5016 for oral suspension.

#### **3.1 SUMMARY OF EFFICACY**

The Applicant considered the efficacy of patiomer was supported by five clinical studies- three studies for the treatment of hyperkalemia and two studies for the prevention of hyperkalemia. The Applicant is only seeking approval for the treatment of hyperkalemia; therefore, this review will primarily focus on the two-part Phase 3 clinical study (RLY5016-301). Efficacy was assessed in all studies using endpoints based on serum potassium.

Study RLY5016-301 was a two-part, single-blind, single arm, Phase 3 study evaluating the efficacy and safety of patiomer for the treatment of hyperkalemia.

Part A: This was considered the treatment phase of this study and was 4 weeks in duration. Study subjects eligible for Part A had baseline hyperkalemia (serum potassium of 5.1 to <6.5mEq/L) and CKD (estimate glomerular filtration rate [eGFR] of 15 to <60 mL/min/1.73m<sup>2</sup>) and were on stable doses of at least one Renin–Angiotensin–Aldosterone System Inhibitor (RAASi) medication- a total of 243 patients. The primary efficacy endpoint for Part A was the change in serum potassium from the Part A Baseline to Part A Week 4 visit. The mean change in serum potassium was -1.01 (0.031) mEq/L (95% CI: [-1.07, -0.95]) and was statistically significantly different from zero ( $p < 0.001$ ). The secondary endpoint of Part A was the proportion of subjects with a serum potassium level in the target range (3.8 to <5.1mEq) at week 4. The proportion of subjects within the target potassium range at week 4 was 76% (95% CI: [70%, 81%]). The results from Part A demonstrate that treatment with patiomer at a starting dose of 4.2 or 8.4 g twice daily (chosen according to screening serum potassium level and followed by titration when necessary according to the potassium response observed) significantly reduces serum potassium levels.

Part B: Part B is a randomized, placebo-controlled 8 week study starting at the completion of Part A, 4 weeks. This was considered the withdrawal phase of this study, evaluating the effect of withdrawing patiomer on serum potassium control as compared to continued dosing with patiomer. Subjects were eligible for Part B if their Part A baseline serum potassium was  $\geq 5.5$  and, at the Part A week 4 visit, the serum potassium was in the defined target range of 3.8 to 5.1 mEq/L. The subject was then randomized to continue their same daily dose or withdraw the study drug and continue placebo for an additional 8 weeks. Of note, the subject had to remain on their current RAASi at the same dose they were on at week 4 of Part A. The patiomer dose could be modified or

discontinued according to a protocol-specified titration algorithm based on potassium levels. A total of 107 met eligibility and 52 were randomized to receive placebo and 55 were randomized to continue patiomer. The primary efficacy endpoint for Part B was the change from the Part B Baseline serum potassium to either the Part B Week 4 visit, if the subject's serum potassium remained  $\geq 3.8$  mEq/L and  $< 5.5$  mEq/L up to the Part B Week 4 visit, or the earliest Part B visit at which the subject's serum potassium was  $< 3.8$  mEq/L or  $\geq 5.5$  mEq/L. The estimated difference in the median change from the Part B baseline was 0.72 mEq/L (95% CI: [0.46 to 0.99]);  $p < 0.001$  for between-group difference in mean ranks of change). The estimated median change in serum potassium from Part B baseline was an increase of 0.72 mEq/L in the placebo group and 0.00 mEq/L in the treatment group. The secondary endpoints in Part B were the proportion of subjects with serum potassium  $\geq 5.5$  mEq/L (secondary endpoint #1) and  $\geq 5.1$  mEq/L (secondary endpoint #2) at any time through week 8 of Part B. Both secondary endpoints were statistically significant when compared to placebo (#1: 60% placebo versus 15% in the treatment group; #2: 91% in placebo versus 43% in the treatment group).

### **3.2 SUMMARY OF SAFETY CONCERNS**

The overall safety population consisted of pooled data from four studies (RLY5016-205, -301, -202 and -204). The safety population ( $n=734$ ) included subjects with moderate to severe CKD, with or without heart failure and a significant burden of chronic comorbidities and cardiovascular risk factors, including hypertension, diabetes, cardiac arrhythmias and hyperlipidemia.

In the pooled population, 8.3% of subjects reported at least one serious adverse event (SAE). Cardiovascular events, renal events, and infection were the most common types of SAEs, however, they appear to be related to the subject's underlying disease(s). A total of 20 deaths were reported in the drug development program; 18 of these deaths were in subjects receiving study drug. An independent Safety Review Board (SRB) adjudicated all deaths that occurred in the studies and the deaths were assessed as unlikely related to hypo/ hyperkalemia or hypomagnesaemia. Given the comorbidities of the patient population, this number of deaths is not unexpected. The clinical reviewer concurred that the deaths were unlikely related to patiomer.

The most common adverse events (AEs) associated with patiomer were constipation (7.2%), hypomagnesemia (5.3%), diarrhea (4.8%), nausea (2.3%), abdominal discomfort (2.0%) and flatulence (2.0%). AEs that led to permanent discontinuation occurred in 49 (7.4%) subjects in the pooled studies. The most commonly reported reactions leading to discontinuation of patiomer were GI adverse reactions (2.7%), including but not limited to vomiting, diarrhea, constipation and flatulence. The treatment-emergent adverse events (TEAs) observed in the pooled studies were constipation (6.2%), hypomagnesemia (4.5%), and diarrhea (3.0%)<sup>2</sup>. Since this drug is not absorbed, GI AEs are expected and were seen in the development program. These adverse events were common, non-serious TEAs that led to discontinuation.

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<sup>2</sup> Xiao, S. Medical Officer Review for Veltassa (patiomer), dated June 19, 2015

## **Drug-Drug Interactions (DDI)**

Since patiromer is not systemically absorbed, drug-drug interactions arise through binding of the polymer to another orally administered drug in the GI tract. This can lead to a change absorption of the interacting drug and, potentially, to loss of efficacy of the interacting drug.

A biologically-relevant in vitro test system was used to evaluate the potential interaction (i.e. binding) between patiromer and 28 orally administered compounds commonly used in the target patient population. A binding of <30% was considered not clinically meaningful. Any binding  $\geq$ 30% the clinical importance of the potential change in drug exposure has been assessed and the Applicant proposed labeling recommending separating drug administration from patiromer and clinical monitoring of the patient. Fourteen of the 28 drugs tested (50%) bound to patiromer at least 30% (see Table 1.).

Table 1. Patiromer in Vitro Drug Binding

<b>&gt;50% binding</b>	<b>30% - 50% binding</b>
Amlodipine	Clopidogrel
Cinacalcet	Furosemide
Ciprofloxacin	Lithium
Levothyroxine	Metformin
Quinidine	Metoprolol
Thiamine	Verapamil
Trimethoprim	Warfarin

**Reviewer comment:** This DDI interaction potential is the main safety concern of interest, given that half of all the drugs tested had  $\geq$ 30% binding. This risk was assessed in the Applicant's in vitro testing but was not characterized during the safety database, as the studies were not designed to assess this risk. In an effort to mitigate this risk, a once daily regimen is likely to mitigate the risk of a drug-drug interaction, and, according to the clinical pharmacology reviewer, should provide acceptable efficacy in lowering serum potassium levels.

## **4 DISCUSSION**

Patiromer is a cation-exchange (b) (4) proposed for the treatment of hyperkalemia. Patiromer demonstrated clinically and statistically significant reductions in serum potassium levels and enabled the majority of subjects to reach and/or remain in the target range of normal serum level. This potassium lowering effect of patiromer is maintained over time, for at least 12 months.

The most common adverse events were nonserious GI complaints; constipation and diarrhea that started within 4 weeks of initiating therapy, were mild in severity, and resolved with continued treatment. Patiromer, as with other cation-exchange (b) (4) (i.e. SPS), may be associated with other, more significant GI adverse events. SPS labeling contains a warning of intestinal necrosis based on post-approval case reports of fatal and

serious adverse GI events associated with SPS use. The label states that these cases involved the concomitant use of sorbitol and that many of these cases involved patients with other risk factors for intestinal necrosis. Patiromer's label will contain a similar warning to avoid use in patients with severe constipation, bowel obstruction or impaction. Patiromer's label will also point out that although these serious GI events were not seen in the clinical program, patients with a history of bowel obstruction or major GI surgery, severe GI disorders, or swallowing disorders were not included in patiromer's clinical studies.

The major safety concern associated with patiromer is the risk of DDI's due to the potential for patiromer to bind other drugs and limiting their absorption, and therefore, the efficacy of these drugs. The DDI does not affect the efficacy of patiromer. Of the 28 drugs that underwent in vitro screening, seven showed >50% binding to patiromer and another seven showed 30% to 50% binding (see Table 1 in Section 3.2). The labeling will contain a boxed warning regarding the potential risk of DDIs, a Warning and precaution, and counseling recommendations for the prescriber to instruct patients to separate the administration of patiromer from any other oral drug administration by 6 hours. Additionally, the label will advise prescribers that patients should not use patiromer if the spacing strategy is not possible. Similar information is also included in a MG for patients. DRISK recommends incorporating the administration instructions into the container labeling since patiromer is dispensed in unit-of use manufacturer packaging. The review team and Division of Medication Error and Prevention (DMEPA) concurred with this recommendation. Although the final labeling has not been agreed upon, DRISK agrees that the current Agency's proposed labeling for patiromer is sufficient to mitigate the risk of DDI.

## **5 CONCLUSION**

In conclusion, risk mitigation measures beyond labeling are not warranted for Veltassa. Based on the currently available data, the benefit-risk profile for Veltassa is acceptable for the treatment of hyperkalemia and a REMS is not warranted to ensure the benefits outweigh the risks of Veltassa.

Should DCRP have any concerns or questions, or feel that a REMS may be warranted for this product, or if new safety information becomes available, please send a consult to DRISK.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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LEAH M HART-BANKS  
10/21/2015

REEMA J MEHTA  
10/21/2015  
I concur with the conclusion.