

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205739Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	October 9, 2015
From	Aliza Thompson
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 205739
Supplement#	
Applicant	Relypsa
Date of Submission	October 21, 2014
PDUFA Goal Date	October 21, 2015
Proprietary Name / Established (USAN) names	Veltassa/ Patiromer
Dosage forms / Strength	Oral suspension/ packets containing 8.4, 16.8, or 25.2 grams patiromer
Proposed Indication(s)	Treatment of hyperkalemia
Recommended:	Approval pending agreement on labeling and resolution of outstanding CMC issues

This secondary review is based on the following reviews:

Material Reviewed/Consulted	
Quality Assessment (7/28/15)	Raymond Frankewich, Mohan Sapru, Elsbeth Chikhale, Angelica Dorantes, Kasturi Srinivasachar, Vipul Dholakia, Erika Pfeiler, Vipul Dholakia, Michael Folkendt, Michael Trehy, Ilan Geerlof-Vidavsky, Cindy Diem Ngo, Xiaofei Liu, Raanan Bloom
Pharmacology Toxicology Review (6/19/15)	William Link, Albert De Felice
Clinical Pharmacology Review (7/23/15)	Ju-Ping Lai, Jeffry Florian, Rajanikanth Madabushi
Clinical Review (6/19/15)	Shen Xiao
Statistical Review (6/11/15)	Fanhui Kong, Hsien Ming Hung
Division of Medication Error Prevention and Analysis Review (2/12/15)	Janine Stewart, Chi-Ming (Alice) Tu
Office of Scientific Investigations Clinical Inspection Summary (6/22/15)	Sharon Gershon, Susan Thompson

1. Introduction

Patiromer is a non-absorbed cation-exchange polymer that binds potassium in the lumen of the colon. On October 21, 2014, Relypsa submitted a new drug application for patiromer for the “treatment of hyperkalemia.” While there is widespread agreement among members of the review team that the drug is effective in lowering serum potassium levels, the results of *in vitro* drug-drug interaction studies raise concern about the drug’s potential to bind other oral medications, thus limiting their absorption. How best to address and mitigate this risk has been a significant review issue.

2. Background

Disease Background: Hyperkalemia is typically defined as a serum potassium > 5 mEq/L. The extracellular concentration of potassium is tightly regulated by the movement of potassium into and out of cells and urinary excretion. Hence, in the general population, hyperkalemia is reported to be a relatively rare event. Hyperkalemia is typically seen in patients with acute or chronic kidney disease or heart failure, particularly in those who are on renin-angiotensin-aldosterone system inhibitors (RAAS inhibitors). Of note, this population is often on multiple medications, some of which provide important morbidity and mortality benefits.

Marked elevations in serum potassium levels can cause fatal cardiac arrhythmias, conduction abnormalities, muscle weakness and paralysis. Unfortunately, treatment options for removing excess potassium from the body are limited. Sodium polystyrene sulfonate (SPS, Kayexalate), approved in 1958, is the only cation-exchange resin approved in the U.S. for the treatment of hyperkalemia. To date, use of SPS has been limited by tolerability and safety concerns (i.e., colonic necrosis and sodium absorption leading to volume overload) and questions about efficacy. SPS’s potential to bind other co-administered oral medications (the main safety concern for patiromer) has not been evaluated; hence, drug-drug interactions may also be an issue for this product.

Patiromer and its Regulatory History: Patiromer is a cation-exchange polymer¹ that binds potassium in the lumen of the colon, thereby increasing fecal potassium excretion and lowering serum potassium levels. The product is a NME and has never been marketed outside the U.S.

An IND to develop patiromer for the treatment of hyperkalemia was submitted in December 2007. As noted in the Clinical Review, there were a number of discussions with the sponsor over the course of development. Major clinical topics included (b) (4) efficacy endpoints in phase 3, the assay for quantifying the increase in serum potassium due to hemolysis and the potential impact of hemolysis on the efficacy findings in Part A of the applicant’s phase 3 trial, the safety database, dose selection, and the kinetics of patiromer’s effect on serum potassium. The

¹ Calcium ions are exchanged with potassium ions.

Clinical Review contains an overview of these discussions (see pages 13-16) and so I will not repeat them here.

With regard to important milestones and agreements, an End-of-Phase 2 meeting was held in November 2011. Approximately 7 months later, Relypsa submitted a request for special protocol assessment (SPA) of their single phase 3 trial, to which the Agency responded with a SPA no agreement letter. Following further discussion with the Agency, Relypsa submitted a revised protocol, and the Agency issued a SPA-Agreement letter. In March 2014, the sponsor met with the Agency to discuss their topline results and the format and contents of their future NDA submission. Relypsa submitted their NDA for patiomor approximately 7 months later.

3. CMC/Device

At this time, the overall product quality recommendation is pending a satisfactory response to outstanding issues related to elemental impurities in the drug substance and xanthan gum including acceptance criteria, analytical procedures and validation reports. From a Quality perspective, a major issue is the drug's propensity to generate fluoride ion when the drug degrades. According to the Quality review, this risk can be adequately addressed by long-term storage in the refrigerator (i.e., at 2°C to 8°C).

Drug Substance: The patiomor anion (also referred to as RLY5016S) is considered the active moiety since it is the molecular species that binds potassium. Because the patiomor anion is (b) (4) the patiomor anion with the calcium sorbitol counter-ion is proposed as the drug substance. The established name for the active moiety is "patiomor" and for the drug substance is "patiomor sorbitex calcium."

The drug substance is a free flowing off-white to light brown powder composed of individual spherical beads (b) (4)

(b) (4)

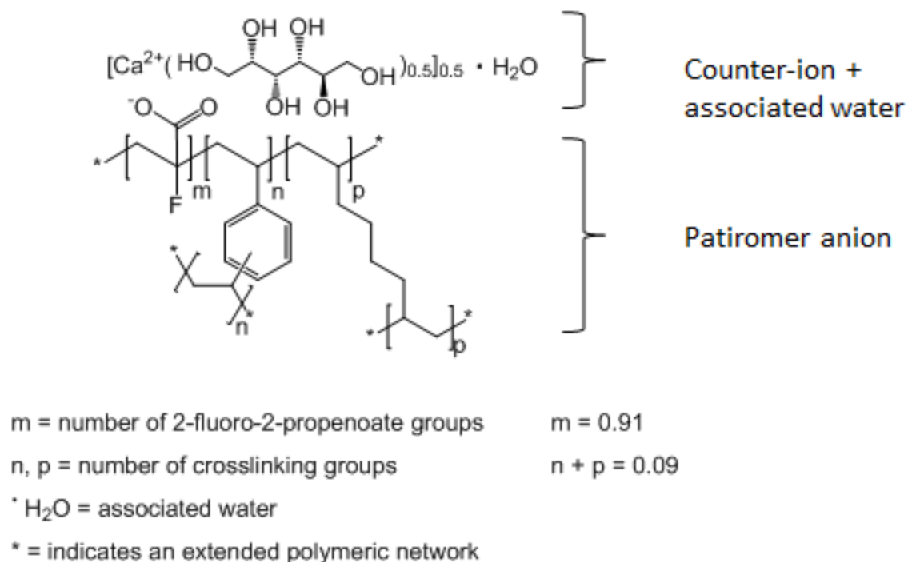


Figure 1: Structural Formula of Patiomer Sorbitex Calcium

The USAN chemical name for patiomer sorbitex calcium

(b) (4)

Each gram of patiomer is equivalent to a nominal amount of 2 grams of patiomer sorbitex calcium.

(b) (4)

Drug Product: The drug product consists of the drug substance formulated with (b) (4) wt% xanthan gum (b) (4). The drug product 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, 16.8 grams or 25.2 grams patiomer.

Expiration Date and Storage Conditions: Stability data indicate that the drug product is stable at the long term storage condition of 2-8° (b) (4).

Based on the available data, a 24-month drug product expiration date is being granted when stored in the refrigerator at 2°C to 8°C (36°F to 46°F). In-use stability studies support storage at room temperature for up to 3 months.

Facilities review/inspection: All inspections have been completed. Drug product and drug substance manufacturing facilities have been deemed acceptable.

4. Nonclinical Pharmacology/Toxicology

According to Dr. Link's review, the preclinical toxicology program was well-conducted and thorough and the application can be approved from a pharmacology/toxicology perspective.

ADME studies: In radiolabeled ADME studies conducted in rats and dogs, there was no significant systemic absorption of patiomer. Quantitative whole-body autoradiography analysis in rats showed that radioactivity was limited to the gastrointestinal tract, with no detectable level of radioactivity in other tissues or organs.

Toxicity studies: No adverse effects were observed in rats or dogs following oral administration at dose levels up to 15-fold the highest dose studied in the applicant's phase 3 trial (50.4 g/day). As previously noted, fluoride ion is generated when the drug degrades; however, according to Dr. Link, the (b) (4) A study conducted in rats to assess the effect of administering the polymer anion (b) (4) confirmed that systemic absorption of fluoride is substantially lower when the (b) (4) as opposed to the (b) (4) is administered orally. Toxicity assessments (literature searches, *in silico* computational analyses and Ames assays) were also performed on other possible drug substance impurities; these assessments did not raise any safety concerns.

Pharmacology: RLY5016 bound potassium in *in vitro* ionic matrices, increased fecal potassium excretion in animals with normal renal function, and lowered serum potassium levels in hyperkalemic rats with impaired renal function. RLY5016 can also bind other cations (e.g., protons, magnesium, calcium and sodium); the extent to which it binds these other cations depends on the local concentration of the cation and its valency. According to Dr. Link, the majority of potassium binding to patiomer occurs in the colon where potassium is the most abundant cation.

Reproductive toxicology: Reproductive and development toxicity was evaluated in a rat fertility study and rat and rabbit teratology studies at maximum feasible dosages. According to Dr. Link, other than nutritionally-related effects on dam's offspring, no effects were noted. As agreed with the Agency, peri/postnatal development studies were not conducted.

Genotoxicity and Carcinogenicity: Patiomer was not genotoxic in the reverse mutation test (Ames assay), chromosome aberration or rat micronucleus assays. Carcinogenicity studies were waived.

5. Clinical Pharmacology/Biopharmaceutics

As previously indicated, patiomer's potential to bind other oral medications has been a significant review issue. Nevertheless, the Office of Clinical Pharmacology believes that this risk can be adequately mitigated with appropriate labeling and is recommending approval. Of note, given the potential for drug-drug interactions, the clinical pharmacology team is recommending a different dosing regimen (b) (4) (i.e., once daily). (b) (4)

General clinical pharmacology: As discussed in Section 4, no significant systemic absorption of patiromer was observed in animal studies; based on these findings, it is assumed that the drug is not significantly absorbed in humans. Accordingly, conventional PK studies and analyses were not performed. Because the drug product is not significantly absorbed, no Thorough QT study was conducted.

Dosing regimen: In the applicant's phase 3 trial, patiromer was administered twice daily and the starting dose of patiromer was adjusted according to the baseline potassium level. Based on their analyses of the data and given the potential for drug-drug interactions, the clinical pharmacology team is recommending once daily (b) (4) and a starting dose of 8.4 g regardless of the baseline potassium level.

- Once daily dosing: Support for the efficacy of a once daily dosing regimen is provided by a phase 1 open-label, multiple-dose crossover study in healthy subjects. In this study, 12 subjects were administered 25.2 grams of patiromer per day orally as a once daily, twice daily or thrice daily regimen for 6 days. As shown in the table below, the three regimens produced similar effects on fecal potassium and urinary potassium excretion. Hence, a QD regimen would be expected to produce a similar serum potassium lowering effect as a BID regimen, provided that the same total daily dose is administered.

Table 1: Effect of QD, BID and TID dosing on fecal potassium and urinary potassium excretion

Variable/Time Point	8.4 g TID (N=12)	12.6 g BID (N=12)	25.2 g QD (N=12)	Overall p-value
Fecal Potassium (mg)				
Baseline	584 ± 244	584 ± 244	584 ± 244	
Endpoint	2134 ± 629	2003 ± 661	1867 ± 540	0.37
Change from Baseline to Endpoint	1550 ± 519	1419 ± 550	1283 ± 530	0.37
Urinary Potassium (mg)				
Baseline	4450 ± 362	4450 ± 362	4450 ± 362	
Endpoint	3010 ± 474	2916 ± 327	3012 ± 446	0.39
Change from Baseline to Endpoint	-1440 ± 384	-1534 ± 295	-1438 ± 384	0.39

Source: Table 3 from Clinical Pharmacology Review, table recreated from Table 5, page 17 of the Applicant's Summary-clin-pharm-0002

- Starting dose: According to the Clinical Pharmacology review, available data do not support the use of a higher starting dose in patients with higher baseline serum potassium levels. In the applicant's phase 2 trial, for the same daily dose of patiromer, subjects with a

higher baseline serum potassium level had a greater reduction in serum potassium by day 3 than subjects with a lower serum potassium level (see Figure 2 below).²

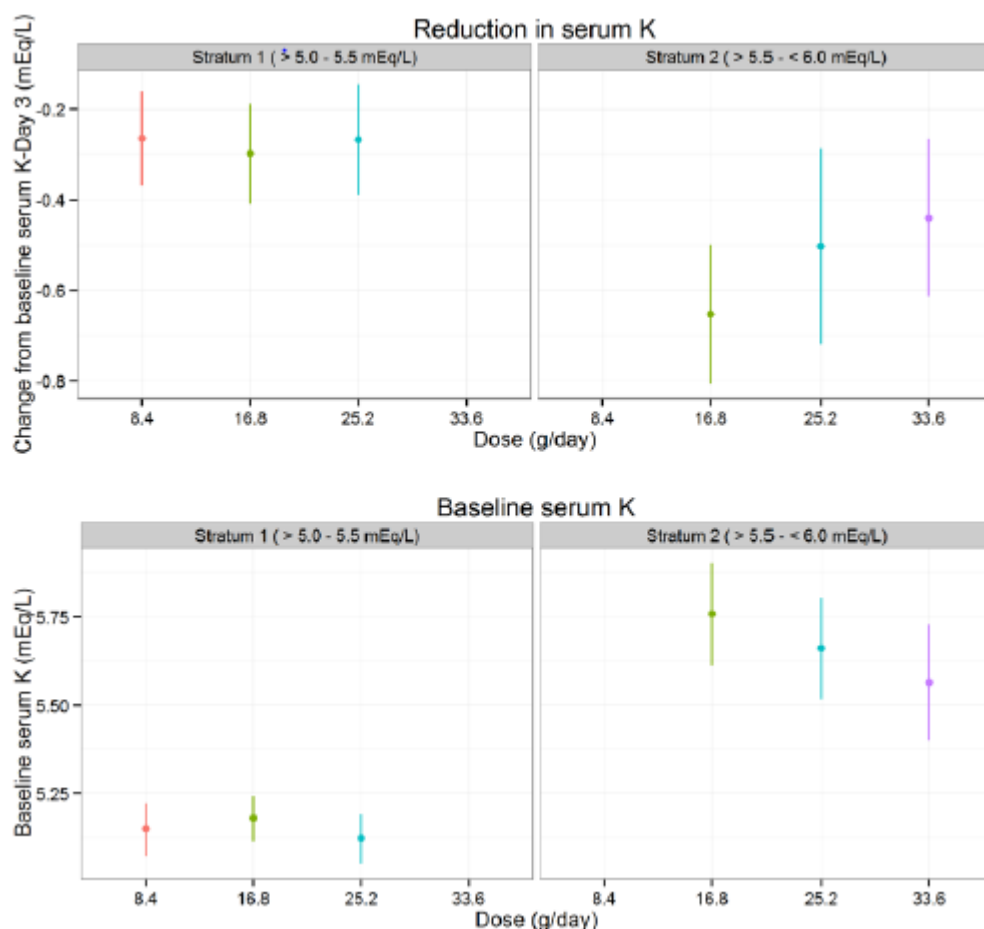


Figure 2: Reduction in serum potassium vs. dose and baseline serum potassium vs. dose in the applicant's phase 2 trial, RLY5016-205

Source: Figure 3, Clinical Pharmacology Review

A mixed model repeated measures analysis of the integrated efficacy data from the phase 2 and 3 trials also showed that the baseline serum potassium level played a much larger role in the change in serum potassium than the interval dose (see table below). Based on these and other analyses (see for example Figure 3 on page 10 of the Clinical Pharmacology Review), the clinical pharmacology team is recommending a starting dose of 8.4 g/day regardless of the baseline serum potassium level.³

² In the phase 2 trial, dose titration was allowed starting on day 3, hence analyses focused on the day 3 value.

³ Of note, in the phase 3 trial and long-term maintenance phase of the phase 2 trial, the mean patiromer dose during treatment was greater in subjects with higher baseline potassium levels as compared to those with lower baseline levels. This observation may reflect the fact that subjects with higher baseline potassium levels were started on a higher dose and up-titration was allowed on Day 3 before the treatment effect had plateaued. Up-titration based on random "highs"/values exceeding the up-titration threshold may have also contributed to this finding.

Table 2: Model-projected mean change in serum potassium (mEq/L) based on baseline serum potassium and interval dose

Baseline Serum K (mEq/L)	Change from baseline serum K (mEq/L)			
	8.4 g/day	16.8 g/day	25.2 g/day	33.6 g/day
5.0	-0.19	-0.22	-0.26	-0.29
5.5	-0.49	-0.52	-0.56	-0.59
6.0	-0.78	-0.81	-0.85	-0.88

Source: Table 1, Clinical Pharmacology Review

- **Dose Titration:** In the applicant's phase 3 trial, the dose of patiromer was titrated based on serum potassium level, assessed starting on Day 3 and then weekly to the end of the 4 week treatment period of Part A, with the aim of achieving a serum potassium in the target range of 3.8 to < 5.1 mEq/L. The applicant's phase 2 trial, RLY5016-205, also permitted dose titration starting on Day 3.

In a study in healthy subjects, a dose-dependent increase in mean daily fecal potassium excretion was observed when patiromer was administered for 8 days (doses of 2.52, 12.6, 25.2 and 50.4 g/day). However, as shown in Table 2 above, analyses of the integrated efficacy data from the phase 2 and 3 trial did not suggest a clinically relevant dose-response relationship over the doses studied. Nonetheless, other analyses performed by Clinical Pharmacology suggest that some patients may ultimately need higher doses to achieve the target range. For further discussion of this issue, as well as the rationale behind the maximum recommended daily dose of 25.2 g/day, see pages 13-14 of the Clinical Pharmacology Review.

As previously stated, in the phase 2 and 3 program, dose titration was allowed as early as Day 3. However, as shown in the figure below and in Figures 5-6 of the Clinical Pharmacology Review, it takes longer than 3 days for the treatment effect to plateau. Based on the available data on the time course of patiromer's effect on serum potassium, the review team is recommending waiting 1-2 weeks prior to up-titration.

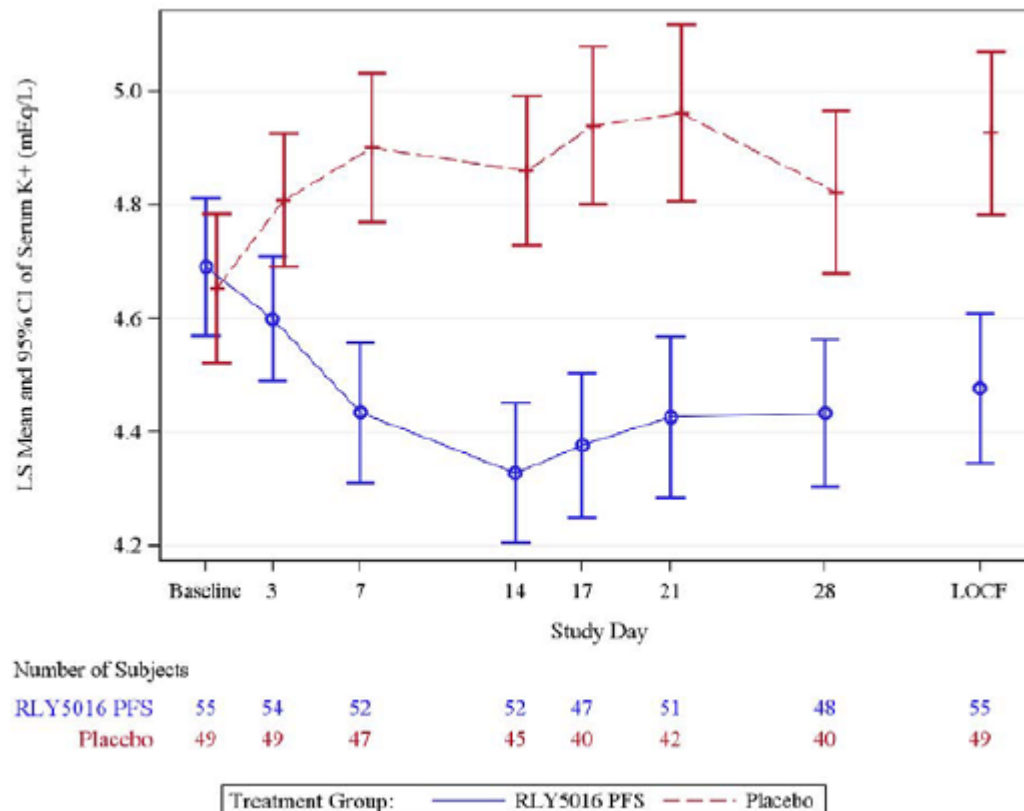


Figure 3: Time course of LS Mean and 95% CI of serum potassium following fixed dosing with 25.2 g/day of patiromer and placebo in heart failure patients (Study RLY5016-202)

Source: Figure 7, Clinical Pharmacology Review, taken from Applicant's Study Report - RLY5016-202

Drug-Drug Interaction: As has been the practice with oral phosphate binders, patiromer's potential to interaction with other oral medications was evaluated via *in vitro* studies. Of the 28 drugs that were tested, approximately half showed a positive interaction (defined as > 30% binding). Rivaroxaban, although it did not meet the 30% threshold, showed 28% binding.

Table 3: Patiromer's Drug-Drug Interaction Potential—Medications that were tested *in vitro* and results of testing

Allopurinol	Cinacalcet	Lisinopril	Rivaroxaban
Amlodipine	Ciprofloxacin	Lithium	Spironolactone
Amoxicillin	Clopidogrel	Metformin	Thiamine
Apixaban	Digoxin	Metoprolol	Trimethoprim
Aspirin	Furosemide	Phenytoin	Valsartan
Atorvastatin	Glipizide	Quinidine	Verapamil
Cephalexin	Levothyroxine	Riboflavin	Warfarin

Green: > 50% binding; Blue: 30% – 50% binding; Red: 28% binding

Source: Slide Set for September 18, 2015 Regulatory Briefing for Patiromer

The Office of Clinical Pharmacology and applicant agree that patiromer should be taken once a day, (b) (4) to mitigate the potential risk of a drug-drug interaction. However, there has been disagreement over what constitutes an adequate window of separation from other orally administered drugs.

In their revised label, received on July 20, 2015, the applicant proposed (b) (4) hour window of separation between patiromer and other medications, based on gastric emptying and gastrointestinal (GI) transit times. During a follow-up teleconference with the applicant on July 21, 2015, Dr. Madabushi agreed that basing the window on expected gastric emptying and GI transit times was reasonable but raised concern that the proposed window may not be adequate in some cases, particularly for patients with diabetic gastroparesis, in whom gastric emptying times are delayed.

In their review dated July 27, 2015, the Office of Clinical Pharmacology recommended that dosing with concomitant medications be separated by at least 6 hours, but also noted that discussions with the applicant were ongoing. Their July 27th review contains the following specific recommendations on dosing with concomitant medications:

- Co-administration of Veltassa® with other drugs should be avoided unless lack of binding to Veltassa® has been demonstrated. When such information is not available maximum separation should be considered given the drug interaction potential.
- If the patient's medications include drugs with a QD dosing regimen, the recommended separation is 12 hours. This recommendation is applicable to situations where the concomitantly administered drugs can be taken together i.e., either in the morning or evening. If the concomitantly administered drugs need to be separated i.e., some taken in the morning and some in the evening, Veltassa® should be administered with lunch i.e., at least 6 hours separation.
- If the patient's medications include drugs with a BID dosing regimen intended for chronic treatment (administered in the morning and evening), Veltassa® should be administered with lunch i.e., at least 6 hours separation.
- If the patient's medications include drugs with a dosing regimen more frequent than BID, a pragmatic separation strategy is not feasible. In such situations, Veltassa® should not be used.

Following the completion of the OCP review, the applicant submitted additional information in support of a (b) (4) hour spacing window. Based on its review of the submission as well as the published literature on gastric emptying of liquids and small particles, the clinical pharmacology review team continues to believe that a (b) (4) hour window of separation is insufficient and recommends a 6-hour spacing window. The review team's conclusion and associated rationale were communicated to the applicant in an advice letter dated September 16, 2015. The clinical pharmacology review team will also file an addendum that addresses the basis for their conclusion.

Time course of Patiromer's potassium lowering effect:

The time to onset of patiromer's potassium lowering effect was evaluated in an open-label, uncontrolled study in 25 hyperkalemic patients with CKD (mean baseline serum potassium of

5.9 mEq/L). The study included a 3-day inpatient potassium-controlled diet run-in period and a 48-hour inpatient potassium-controlled diet treatment period in which subjects were administered four fixed doses of 8.4 grams patiromer (16.8 grams/day). Statistically significant reductions in serum potassium (-0.2 mEq/L) were first observed 7 hours after initiating therapy. Potassium levels declined further during the 48-hour dosing period. In the 4 days following discontinuation of therapy, potassium levels rose. Although the study lacked a control arm, the controlled diet run-in period and continued use of a controlled diet during the treatment period likely limited confounding due to dietary changes during this period.

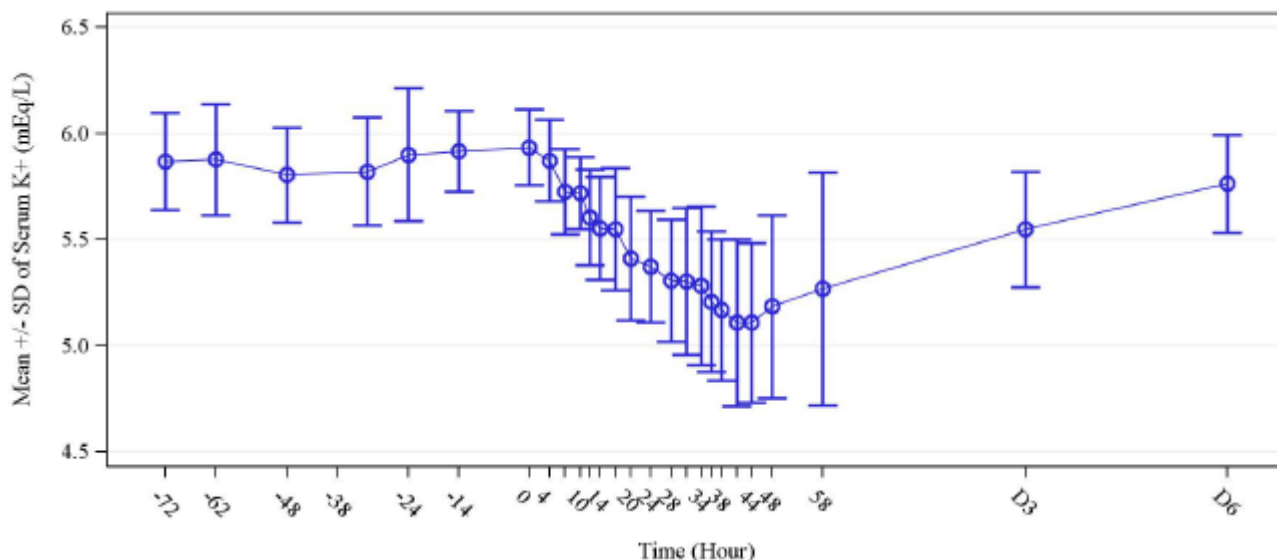


Figure 4: Mean and Standard Deviation of Central Laboratory Serum Potassium (mEq/L) Over Time (Full Analysis Set)

Source: Applicant, Figure 4, Study Report for RLY5016-103

6. Clinical Microbiology

Patiromer is not an antimicrobial therapeutic.

7. Clinical/Statistical- Efficacy

Principal support for efficacy in lowering serum potassium levels is provided by a phase 3 randomized withdrawal trial, RLY5016-301.

Overview of Study Design

RLY5016-301 was a multi-center, phase 3 trial in patients with CKD (eGFR 15- 60 mL/min/1.73m²) and hyperkalemia at screening (serum potassium of 5.1 to < 6.5 mEq/L by local laboratory) who were on a stable dose of at least one RAAS inhibitor for at least 28 days.

The trial consisted of two parts: a single arm, single-blind, 4 week, open-label titration phase (Part A) and a single-blind randomized withdrawal phase (Part B).⁴

⁴ Subjects were blinded to their treatment assignment; Investigators, the site staff and the sponsor were unblinded.

- In Part A, subjects were initiated on patiromer at 4.2 g twice a day or 8.4 g twice a day, depending on the subject's screening serum potassium level. Starting on Day 3 of treatment in Part A, the dose could be titrated based on the local laboratory serum potassium value.
- Subjects who met all of the following criteria were eligible for Part B: had completed the Part A treatment phase on a dose of 8.4 to 50.4 gm per day patiromer; had a Part A baseline central potassium ≥ 5.5 mEq/L; had a local laboratory measured serum potassium value of 3.8 to < 5.1 mEq/L at the Part A Week 4 Visit while receiving treatment with a RAAS inhibitor.

In Part B, the subset of subjects who met the aforementioned entry criteria were randomized to placebo or continued treatment with patiromer for 8 weeks. Subjects randomized into the patiromer treatment arm continued on the same daily dose of patiromer they were on at the Part A Week 4 Visit with dose titration as needed.

The primary efficacy endpoint for Part A was the change in serum potassium (central laboratory) from the Part A baseline to the Part A Week 4 visit. The primary efficacy endpoint for Part B was the change in serum potassium (central laboratory) from the Part B baseline to either:

- Week 4, for subjects whose local serum potassium remains in the range of 3.8 to < 5.5 mEq/L up to week 4⁵; or
- An earlier time point when the subject first has a local serum potassium < 3.8 mEq/L or ≥ 5.5 mEq/L

Secondary endpoints also assessed effects on serum potassium.

An overview of the trial is provided in the figure below.

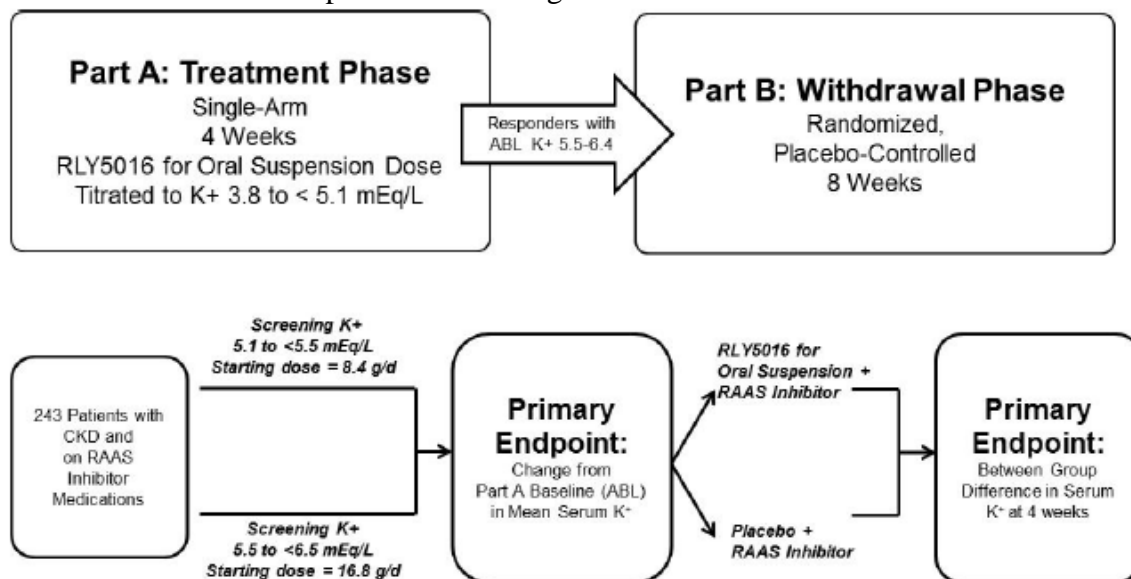


Figure 5: Overview of Study RLY5016-301

⁵ Although Part B was 8 weeks long, the endpoint was the 4-week value (or an earlier time point as specified above).

Statistical Considerations

Analysis Population: The analysis population for efficacy endpoints in Part A consisted of subjects who took one or more doses of patiomer. The analysis population for efficacy endpoints in Part B consisted of subjects who met eligibility criteria for Part B and were randomized into Part B.

Primary Endpoint Analysis:

- The primary endpoint in Part A was tested using a longitudinal repeated measures model that included binary covariates for the presence of heart failure at baseline (yes/no) and type 2 diabetes at baseline (yes/no), and the serum potassium level at the Part A baseline as a continuous covariate.
- An analysis of variance (ANOVA) model with strata used at randomization (abnormal serum potassium [two levels for 5.5 to < 5.8 and ≥ 5.8 mEq/L] and presence of type 2 diabetes) was used to compare the treatment groups and estimate a mean difference in ranks.

Sample Size/Power Considerations: The sample size for Part B assumed a mean difference of 0.48 mEq/L in the change in serum potassium between the placebo and patiomer groups and a standard deviation of 0.40 and that the treatment groups would be compared using Hodges-Lehmann test of the median difference in changes. A sample size of 40 in each group gave over 90% power to test the difference in the median change at a two-sided Type I error rate of 0.05. The sample size in Part A was driven by the plan to have at least 90% statistical power for the primary endpoint in Part B.

Reviewer's comment: At the End-of-Phase 2 meeting, the Agency told the sponsor that RLY5016-301 as designed (with an open-label treatment phase followed by a randomized withdrawal phase) could be considered two distinct trials. Subsequent to that meeting, concern arose about whether Part A of the trial could serve as one of two "adequate and well controlled" trials supporting efficacy given the limitations of the assay for quantifying the increase in serum potassium due to hemolysis and the potential impact of hemolysis on the efficacy findings in Part A.

To mitigate the potential impact of false negative hemolysis assay results on the primary endpoint results for Part A and ensure interpretability of Part A, the sponsor proposed a targeted mean serum potassium decrease from baseline in Part A of at least 0.7 mEq/L with a p-value of less than 0.05. According to the sponsor's analyses, the hemolysis assay used in the trial had a 97.5% probability to detect a change in serum potassium of > 0.36 mEq/L in samples flagged by the assay as "negative" for hemolysis. The proposed targeted mean decrease of at least 0.7 mEq/L was based on a doubling of the serum potassium value of 0.36 mEq/L.

The Division agreed that a change of the proposed magnitude would be sufficient to ensure interpretability, noting the low probability that hemolysis in samples flagged as "negative" could lead to potassium levels increased by as much as 0.36 mEq/L, which was small relative to the expected magnitude of the treatment effect.

Study Results

Demographics

The baseline demographics of subjects in Parts A and B of the trial are shown in Tables 6-11 of the Clinical Review. In Part A, the mean age was 64 years, 58% of subjects were men and 98% were white. Approximately 97% had hypertension, 57% had type 2 diabetes, 42% had heart failure, 25% had a prior myocardial infarction, and 45% had stage 4 or higher CKD. With regard to medication use, 70% of subjects in Part A were on an ACE inhibitor, 38% were on an ARB, 9% were on an aldosterone antagonist, 17% were on dual RAAS blockade and 54% were taking a non-RAAS inhibitor diuretic (thiazide or high ceiling diuretics). As previously discussed, a subset of subjects from Part A enrolled into Part B. For the most part, the aforementioned demographic characteristics, co-morbid conditions and medication use of subjects enrolled into Part B were similar to those of subjects enrolled into Part A.

Few subjects were enrolled from sites in the U.S. Of the subjects enrolled in Part A, 64% were enrolled at sites in Eastern Europe that were not part of the EU, 27% were enrolled at sites in the EU and 9% were enrolled at sites in the US. Of the subjects enrolled in Part B, approximately 4% were enrolled at sites in the US, 79% were enrolled from sites in Eastern Europe that were not part of the EU and approximately 17% were enrolled from sites in the EU.

Disposition

Subject disposition is shown in Tables 12-14 of the Clinical Review. Out of a total of 243 subjects, 219 (90%) completed Part A. The most common reason for not completing Part A was an adverse event, which was reported in 4% of subjects. Of the 107 subjects randomized in Part B, 82% of subjects randomized to patiromer completed Part B as compared to approximately 58% of subjects randomized to placebo. The most common reason for not completing Part B in the placebo arm was meeting a protocol specified withdrawal criteria for a high serum potassium value. Otherwise, the reasons for discontinuation were similar in the two treatment arms.

Primary Endpoint

The trial met the prespecified primary endpoint in Part A. The overall mean (SE) change in serum potassium from the Part A Baseline to Part A Week 4 was -1.01 (0.03) mEq/L (95% CI: -1.07, -0.95). Thus, the mean change exceeded the threshold that was set to address the potential impact of hemolysis (i.e., a mean serum potassium decrease from baseline in Part A of at least 0.7 mEq/L). As in other studies, a larger effect was seen in subjects with higher baseline potassium levels.

Table 4: Change in Serum Potassium (mEq/L) in Part A

	Baseline Potassium		Overall Population (n=237)
	5.1 to < 5.5 mEq/L (n=90)	5.5 to < 6.5 mEq/L (n=147)	
	Serum Potassium (mEq/L)		
Baseline, mean (SD)	5.31 (0.57)	5.74 (0.40)	5.58 (0.51)
Week 4 change from baseline, Mean ± SE (95% CI)	-0.65 ± 0.05 (-0.74, -0.55)	-1.23 ± 0.04 (-1.31, -1.16)	-1.01 ± 0.03 (-1.07, -0.95)
p-value			< 0.001

Source: Statistical Review. See Dr. Kong's statistical review for additional information on the longitudinal model used to derive the estimates.

The trial also met the prespecified primary endpoint in Part B, as shown in the tables below. The estimated difference in the median change from the Part B baseline (placebo minus patiromer) was 0.72 mEq/L ($p < 0.0001$).

Table 5: Change in Serum Potassium from Part B Baseline to Part B Week 4 or the First Local Laboratory Serum Potassium Result of < 3.8 mEq/L or \geq 5.5 mEq/L

	Placebo n=52	Patiromer n=55
Baseline, mean (SD)	4.45 (0.34)	4.49 (0.43)*
Estimated Median Change in Serum K (quartiles)	0.72 (0.22, 1.22)	0 (-0.3, 0.30)
Difference in Median change Estimate (95% CI)	0.72 (0.46, 0.99)	
p-value	<0.001	

Source: Statistical Review (Table 3.6) and Clinical Review (Table 17)

*n based on 54.

Secondary Endpoints

The prespecified secondary endpoints for Part B were (1) the proportion of subjects with a serum potassium \geq 5.5 mEq/L at any time (post Part B Baseline) through the Part B Week 8 visit and (2) the proportion of subjects with a serum potassium \geq 5.1 at any time (post Part B Baseline) through the Part B Week 8 visit. As shown in the table below, a greater proportion of subjects in the placebo arm, as compared to the patiromer arm, had a serum potassium value exceeding these thresholds.

Table 6: Secondary endpoints in Part B: Proportion of subjects with a serum potassium concentration above the specified value at any time (post Part B Baseline) through the Part B Week 8 Visit

Secondary endpoint	Stratified Percentage (95% CI)			p-value
	Placebo n=52	Patiromer n=55	Difference	
Serum K \geq 5.5	60 (47, 74)	15 (6, 24)	45 (29, 61)	<0.001
Serum K \geq 5.1	91 (83, 99)	43 (30, 56)	48 (33, 63)	<0.001

Source: Statistical Review, Table 3.6

The prespecified secondary endpoint in Part A was the proportion of subjects with a centrally measured serum potassium level that was in the Part A target range (3.8 to < 5.1 mEq/L) at the Part A Week 4 visit. According to the Clinical Review, the proportion of subjects with a serum potassium level in this range at Week 4 was 76% (95% CI: 70%, 81%); the proportion was similar in the group with a baseline serum potassium of 5.1 to < 5.5 mEq/L and in the group with a baseline serum potassium of 5.5 to < 6.5 mEq/L.

Persistence of Efficacy

Data on persistence of efficacy during long-term administration is provided by Study RLY5016-205, a phase 2 dose-ranging study with a long-term open label treatment phase. In this study, patients with type 2 diabetes, chronic kidney disease (eGFR 15 to <60 mL/min/1.73m²), and hyperkalemia while on a RAAS inhibitor were treated for up to 52 weeks with patiromer. As shown in Figure 6 below, the reduction in serum potassium that was achieved in the days to weeks following initiation of therapy was maintained during the treatment period. Upon discontinuation of therapy at week 52, serum potassium levels rose, although they did not, on average, reach pretreatment levels.

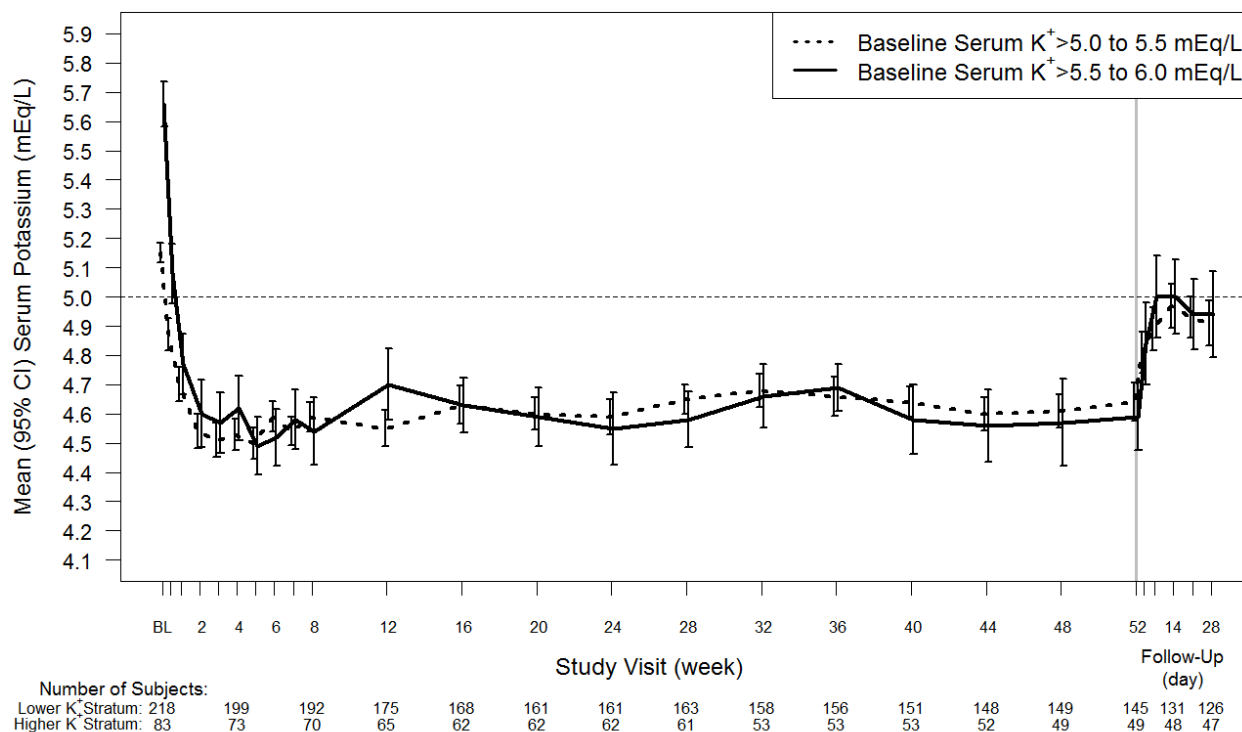


Figure 6: Potassium concentration over time in Study RLY5016-205

Source: Applicant's proposed label

8. Safety

Exposure

According to Dr. Xiao's review, 734 subjects were exposed to at least one dose of RLY5016 in clinical trials. A total of 547 unique subjects with hyperkalemia were treated in phase 2 and phase 3 trials, while a total of 119 unique subjects without hyperkalemia but with risk factors for hyperkalemia (i.e., chronic kidney disease and/or heart failure) were treated with RLY5016 in prevention trials. 149 subjects were treated for 1 year; all of these subjects were enrolled in trial RLY5016-205.

Safety topics of interest

In his review, Dr. Xiao focuses on potential risks of patiomer given the drug's mechanism of action, CMC and preclinical data, and the experience with another member of the pharmacologic class (sodium polystyrene sulfonate). These potential risks include adverse GI effects, hypokalemia, non-specific binding to other cations such as magnesium, and systemic absorption of fluoride and calcium. Although patiomer's potential to interact with other oral medications is the most significant safety concern, the safety data base could not be used to explore this issue given its limitations (i.e., the size and duration of the clinical trials and the lack of a control arm).

Findings related to potential risks of patiomer are summarized below. Unless otherwise noted, the findings reported below are based on the pooled safety database.⁶ Since the amount of controlled safety data is quite limited, the text that follows describes the safety findings in subjects who were treated with patiomer and does not discuss these findings in the context of a comparator/control arm.⁷

Reviewer's Comment: During development, the Agency advised the sponsor to consider ways to obtain controlled safety data in their phase 3 program, but also stated that the nature and size of the safety database needed to support approval depended upon whether the product was systemically absorbed.

GI tolerability and safety: Constipation and diarrhea were among the most common adverse reactions and were reported in 7.2% and 4.8% of subjects treated with patiomer, respectively. Nausea, flatulence and vomiting were each reported in approximately 2% of subjects. In trial RLY5016-202, a double-blind, placebo-controlled trial in heart failure patients, the incidence of GI adverse events, including flatulence, constipation, diarrhea, and vomiting, was higher in the patiomer as compared to placebo arm, suggesting a causal relationship (see Table 40 of the Clinical Review).

According to Dr. Xiao's review, most GI AEs occurred early after starting treatment, were mild in severity, and resolved with continued treatment. Review of the clinical trial data did not reveal any obvious cases of severe, drug-related GI toxicity and did not raise concern for palatability/tolerability issues leading to premature discontinuation of study medication.

Hypokalemia: For the most part, analyses of the adverse event and laboratory data were reassuring as relates to the risk of hypokalemia. As previously noted, serum potassium levels were monitored in the phase 3 and phase 2 trial, and therapy was titrated based on serum potassium levels.⁸

Hypokalemia did not appear to play a role in any of the deaths and no subject had an SAE of hypokalemia. Treatment discontinuations because of hypokalemia also were uncommon. According to Dr. Xiao's review less than 1% of subjects discontinued from studies because of hypokalemia events and under 2% of subjects treated with patiomer were withdrawn because they met the protocol-specified withdrawal criteria.

⁶ The pooled safety dataset included studies RLY5016-205 and -301 as well as two studies that evaluated RLY5016 for the prevention of hyperkalemia (see page 63 of the Clinical Review for additional information). As noted in Dr. Xiao's review, these four studies enrolled patients with underlying CKD and/or heart failure and studied dosing regimens relevant to labeling.

⁷ Controlled safety data is provided by Trial RLY5016-202, a double-blind, randomized trial in which heart failure patients were administered a fixed dose of patiomer 15 g twice daily (n=56) or placebo (n=49) for 28 days. Safety findings in this study are discussed in the Clinical Review. Strictly speaking, the randomized withdrawal phase of the phase 3 trial also provides controlled safety data, however because patients who entered the randomized withdrawal phase had been previously treated with patiomer (and tolerated the therapy), it is difficult to interpret these data.

⁸ In both the treatment initiation period of Study RLY5016-205 and in the open-label treatment phase of the phase 3 trial, serum potassium was measured on day 3, and then at weekly visits (Week 1, 2, etc). During the long-term maintenance phase of Study RLY5016-205, serum potassium was measured every 4 weeks.

Approximately 4.7% of subjects (n=31) in the pooled safety set had a treatment-emergent serum potassium value < 3.5 mEq/L. The percentage of subjects was somewhat higher in the phase 2 trial (5.9 %; n=18) and somewhat lower in the phase 3 trial (3.2%; n=8). Less than 1% of subjects (n=3, all from study 205) had a serum potassium value of 3.0 mEq/L and no subject had a treatment emergent, on-study serum potassium value < 3.0 mEq/L.

Hypomagnesemia: Serum magnesium levels were assessed at screening and/or at baseline in the phase 3 trial and in Study RLY5016-205. Patients with a serum magnesium < 1.4 mg/dL at screening were excluded from the phase 3 trial. In contrast, study RLY5016-205 did not specify an exclusion criterion related to the baseline serum magnesium level. In the treatment initiation period of Study RLY5016-205, serum magnesium levels were measured every two weeks; during the long-term maintenance phase, serum magnesium was measured every 4 weeks. In the phase 3 trial, magnesium levels were measured on day 3 and then at weekly visits.

AEs of hypomagnesemia were not uncommon-- AEs of hypomagnesemia were reported in 5.3% of subjects and AEs of blood magnesium decreased were reported in 0.8%. In Study RLY5016-205, AEs of hypomagnesemia were reported in both the treatment initiation period (3% of subjects) and also during the long-term maintenance period (7.3% of subjects). Hypomagnesemia did not appear to play a role in any of the deaths and no subject had an SAE of hypomagnesemia or permanently discontinued treatment with patiromer because of an AE of hypomagnesemia. With regard to laboratory findings, 1.9% of subjects (n=12) had a magnesium values < 1.2 mg/dL as their lowest post-baseline value after having had a normal or high value at baseline. No subject had a serum magnesium value < 1.0 mg/dL.

Fluoride: In Study RLY5016-205, serum fluoride was measured at baseline, Weeks 4, 8, 24, Week 52 or end-of treatment. In Part A of the phase 3 trial, serum fluoride was measured at screening and Week 4 or end-of treatment; in Part B, serum fluoride was measured at Week 4 and Week 8 or end-of treatment.

Mean (SD) baseline serum fluoride levels were (b) (4) in subjects treated with patiromer in the pooled safety set. At Weeks 4 and 8, mean (SD) serum fluoride concentrations had increased by (b) (4), respectively.⁹ Mean fluoride levels over time in Study RLY5016-205 are shown in the table below. Fluoride levels did not appear to continue to increase over time during continued therapy.

⁹ Source Table 8.3.6.1.1, Applicant's Integrated Summary of Safety

Table 7: Mean Fluoride Levels (ng/mL) Over Time in Study RLY5016-205

	Number	Mean (SD)
Baseline	276	(b) (4)
Week 4	260	
Week 8	249	
Week 24	210	
Week 52	148	
Week 52/ET	152	

Source: Reviewer's analysis; dataset: adlb3

According to Dr. Xiao's review, no subject developed a serum fluoride level (b) (4) (according to the published literature, exposures over this level may lead to adverse effects if maintained for months to years), and no fluoride accumulation related AEs were observed in a study of up to one year duration.

Hypercalcemia: Patiromer has the potential to increase calcium absorption, since calcium ions are exchanged with potassium ions. As discussed on pages 79-81 of Dr. Xiao's clinical review, analyses of laboratory and adverse event data did not suggest that patiromer causes a clinically relevant effect on serum calcium levels.

Other findings: Beyond these risks, there were no other notable safety findings. In the absence of a control/comparator arm, interpretation of data pertaining to deaths, SAEs, discontinuations due to adverse events and common adverse events is limited.

- **Deaths and SAEs:** The clinical review contains a discussion of deaths and SAEs in the development program. For the most part, the reported events are not unexpected events in the trial population. As discussed in Dr. Xiao's review, an independent Safety Review Board (SRB) adjudicated all deaths and provided a determination of the relationship of each death to either hyperkalemia or hypokalemia. The SRB assessed 19 subject deaths as unlikely related to hypo- or hyperkalemia. The relationship between the serum potassium level and death could not be evaluated in one subject because no recent serum potassium value was available.
- **Discontinuations for adverse events:** Discontinuations for adverse events did not appear to be a major issue. According to the Clinical Review, adverse events leading to permanent treatment discontinuation were reported in approximately 7%, of subjects in the pooled safety data set, 5% of subjects in Part A of the phase 3 trial, and 9% of subjects in the phase 2 trial.
- **Common adverse events:** In the pooled safety population, the most common adverse events were constipation (7.2%), hypomagnesaemia (5.3%), renal failure chronic (5.4%), diarrhea (4.8%), hypertension (4.7%). For the most part, adverse events that were reported in the trials would be considered "expected" events in the trial population.

9. Advisory Committee Meeting

The application was not referred to an FDA advisory committee because the clinical trial design and efficacy endpoints are acceptable. Although the drug's potential to bind other oral medications represents a significant safety concern, it was felt that internal expertise was needed to address this issue. Accordingly, as discussed below, a Regulatory Briefing was held to discuss the strategy used to evaluate patiromer's drug-drug interaction potential and appropriate measures to mitigate risk.

10. Pediatrics

The NDA was submitted and filed by the Division prior to reaching an agreed upon pediatric study plan; nonetheless, the pediatric study plan that was submitted to the IND in early October 2014 was felt to be sufficient to initiate a review.

Key conclusions reached to date include the following:

- Given its mechanism of action, patiromer is expected to be effective in lowering serum potassium levels in pediatric patients with chronic kidney disease and hyperkalemia, hence extrapolation of efficacy is acceptable.
- No further animal studies are needed prior to conducting studies in children.
- The specific quantities of all excipients (including xanthan gum) and ingredients in the oral suspension do not raise any safety concerns in pediatric patients down to birth.
- Dosing in all pediatric age groups will be based on body weight as opposed to body surface area. The drug will also be dosed once daily to mitigate the risk of drug-drug interactions.
- Treatment will continue for up to (b) (4), allowing for titration and discontinuation as needed.

The current pediatric plan (submitted on July 9, 2015) consists of two studies to evaluate the pharmacodynamic effects, safety, and tolerability of RLY5016, one in children 2 to 18 years of age with hyperkalemia and one in children 0 to < 2 years of age with hyperkalemia. The review team believes that, as a whole, the proposed studies, which are described in greater detail in the PeRC PREA template for patiromer, are reasonable and will provide the data needed to assess safety and tolerability and support dosing and administration in pediatric patients with hyperkalemia.



11. Other Relevant Regulatory Issues

Financial disclosures: The applicant has adequately disclosed financial arrangements with clinical investigators. These arrangements do not raise concern about the integrity of the data.

DSI audits: Three foreign clinical investigator site inspections and a sponsor inspection were conducted. According to Dr. Gershon's review, no regulatory violations were observed during the sponsor inspection or during inspections at the clinical investigator sites. All inspections were classified as NAI.

Regulatory Briefing: A regulatory briefing was held on September 18, 2015 to address patiomer's drug-drug interaction potential. At the meeting, the Division asked for the committee's input on four questions:

1. Was the strategy for evaluating patiomer's drug-drug interaction potential rational?
2. Had the review team identified a reasonable strategy to mitigate the risk of drug-drug interactions with patiomer?
3. Should further studies be done prior to or after approval to address patiomer's drug-drug interaction potential?
4. Should patiomer be approved?

In general, members of the committee thought that the strategy used to evaluate patiomer's drug-drug interaction potential was reasonable. There was debate about whether there should be a Boxed Warning about the risk of a drug-drug interaction. As far as I could tell, the main concern was that the presence of a Boxed Warning on the patiomer but not the sodium polystyrene sulfonate label would shunt use from patiomer to a product with a less well-characterized safety and efficacy profile. Although the Division indicated that steps would be taken to incorporate similar risk information in the sodium polystyrene sulfonate label, questions were raised about the ability to do so (at all or in a timely manner). There was lack of consensus on whether clinical studies were needed to evaluate patiomer's drug-drug interaction potential. In contrast, there was consensus that the benefits of the product outweigh its risks and that the product should be approved.

12. Labeling

Patiomer's potential to bind other oral medications: Based on the available data and the recommendations of the review team, I believe patients should be instructed to: (1) separate administration of patiomer and other oral medications by 6 hours and (2) not use patiomer (or the other medication) if this spacing strategy is not possible. I also believe that both a

Medication Guide and a Boxed Warning are needed to adequately mitigate the risk of a drug-drug interaction. I discuss my rationale for these recommendations in Section 13. At this time, the applicant has agreed to a Boxed Warning, Medication Guide and a 6-hour spacing window. However, agreement has not yet been reached on the text of the Boxed Warning and text in other sections of the label pertaining to drug-drug interactions. Of note, the Patient Labeling Review of the Medication Guide and Instructions for Use was finalized by Karen Dowdy and Puja Shah on October 8, 2015. The Office of Prescription Drug Promotion Review of the prescribing information was also finalized by Dr. Shah on October 8, 2015. I have yet to review these documents but will do so.

Other issues: At this time, the review team and applicant are aligned on the use of a once daily regimen to mitigate the risk of drug-drug interactions, the starting dose and maximum dose and titration strategy (i.e., titration increments and time interval between titrations). There is also agreement that the strengths will be based on the active moiety in accordance with the USP salt nomenclature policy and that the equivalency statement for the salt will be presented on the back panel of the carton. The proposed proprietary name, Veltassa, has been deemed acceptable by the Office of Medication Error Prevention and Risk Management.

13. Recommendations/Risk Benefit Assessment

- *Recommended Regulatory Action*

Approval pending agreement on labeling and resolution of outstanding CMC issues.

- *Risk Benefit Assessment*

The applicant's clinical development program demonstrated that patiromer is effective in lowering serum potassium concentrations in patients with hyperkalemia, an accepted surrogate endpoint in this population. The estimated difference in the median change from the Part B baseline (placebo minus patiromer) in the randomized withdrawal phase of the phase 3 trial was 0.72 mEq/L. This finding was highly statistically persuasive ($p < 0.0001$) and substantiated by the results of the initial open-label treatment phase of the trial, as well as by the results of a phase 2 dose-ranging trial with a long-term maintenance phase.

From a safety perspective, the main concern has been patiromer's potential to bind other oral medications, thus limiting their absorption. An *in vitro* assay was used to test patiromer's potential to bind other oral medications. Of the 28 drugs that were tested *in vitro*, approximately half showed a positive interaction.

While there have been a range of opinions on how to mitigate this risk, I think there is general consensus about the key concepts. Specifically, (1) the dosing strategy should be simple, feasible, and widely applicable to the range of products a patient may be taking; (2) the associated message in physician and patient label should also be simple; and (3) the risk mitigation strategy should address the fact that multiple physicians may be prescribing medications to patients.

As there is consensus that a Medication Guide is needed (and that a REMS is not an appropriate tool), I won't touch upon this issue further. Instead, I will focus on other issues that have been raised during internal discussions, namely, (1) what constitutes an appropriate spacing window; (2) whether to distinguish between oral medications that have and have not been cleared by *in vitro* studies; (3) whether a Boxed Warning is needed; and (4) whether the product should be approved for short-term use only.

- *Spacing window:* Based on their review of information submitted by the applicant, as well as the published literature, the clinical pharmacology review team is recommending a 6-hour window of separation from concomitant oral medications. Their recommendation is based on a number of considerations including gastric emptying times reported in the published literature, the impact of food on gastric emptying, the fact that some patients may have delayed/prolonged gastric emptying (i.e., diabetic gastroparesis), and the time period for absorption of extended-release products.¹⁰ While a 6-hour separation window is not possible for oral medications administered more frequently than twice a day (and hence the proposed regimen does not allow for use with medications that require such frequent administration), most medications that are used in the target population are expected to be administered once or, at most, twice daily.
- *Distinguishing between oral medications that have and have not been "cleared":* Although the list of oral medications that have been "cleared" by *in vitro* studies should be included in Section 7 of labeling, there is consensus among team members that we should keep the message simple and hence easier to communicate by recommending a single separation strategy for all medications (i.e., separate by 6 hours).
- *Boxed Warning:* According to Agency Guidance, a Boxed Warning is ordinarily used when there is a "serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug." I think the *in vitro* findings to date, which show a positive interaction with ~50% of the drugs that were tested, raise significant concerns about the potential for clinically significant interactions between patiomer and other oral medications. I also believe that with appropriate use of the drug (i.e., appropriate spacing with other oral medications), serious drug-drug interactions can be prevented. Hence, I believe, and the team believes, a Boxed Warning is warranted.
- *Short-term use:* Approving the product for short-term use would mitigate the risk of a drug-drug interaction by limiting the window for interactions and would also lessen concerns about long-term coordination of care (i.e., that some of the patient's physicians may not be aware that the patient is on patiomer or be familiar with the product's drug-drug interaction potential). Although this approach has some appeal, I do not support it. There is unmet need for therapies that can be used chronically to treat hyperkalemia and significant interest in using such therapies to enable use of RAAS inhibitors in patients who might benefit from these agents but cannot otherwise take them because of hyperkalemia. Based on the available data, I believe the decision to use patiomer chronically should be left to the patient and prescriber. Indicating patiomer for short-term

¹⁰ As previously noted, the clinical pharmacology review team plans to file an addendum that documents the basis for the proposed 6-hour window.

use also seems problematic since the indication statement for sodium polystyrene sulfonate, a product that may share this liability, does not refer to a duration of use or specify short-term administration.

Beyond the potential for drug-drug interactions, no other major safety concern has been identified. Potential risks of patiomer given the drug's mechanism of action, preclinical data, and the experience with another member of the pharmacologic class (sodium polystyrene sulfonate) include adverse GI effects, hypokalemia, non-specific binding to other cations such as magnesium, and systemic absorption of fluoride and its counter-ion (calcium). Analyses of laboratory and adverse event data were, for the most part, reassuring as relates to these risks.

In conclusion, I believe the benefits of the product outweigh its risks and that patiomer should be approved for the treatment of hyperkalemia once agreement is reached on labeling and the outstanding CMC issues are resolved.

- *Recommendation for Postmarketing Risk Evaluation and Management Strategies*

None.

- *Recommendation for other Postmarketing Requirements and Commitments*

There have been a range of opinions on whether further studies are needed post-approval to address the potential risk of drug-drug interactions. Some have argued that clinical studies are needed to confirm/determine the relevance of the *in vitro* findings and/or to evaluate whether a 6-hour spacing window is appropriate (i.e., whether, on the one hand, it is sufficient and whether, on the other hand, it can be shortened).

While I think it is important for the applicant to consider conducting further studies to investigate the drug-drug interaction liability of their product, at this time I do not support issuing a PMR to conduct clinical studies. According to the clinical pharmacology review team, a 6-hour spacing window is sufficient to mitigate the risk of a drug-drug interaction. It is also not obvious to me what actions we would take based on the results of some of the proposed studies. Even if the applicant were to show that the positive *in vitro* binding results for some of the tested medications are not clinically relevant, the implications of this finding for the universe of oral medications that have not been tested remains unclear. I also do not believe that showing that the spacing window can be shortened for particular medications is helpful, since I think we need to keep the message about spacing simple and not vary the window by medication. Finally, I am struck that even if the applicant were to demonstrate that a shorter spacing window is appropriate for all immediate release products, the use of extended release products in the target population may prevent us from shortening the window.

- *Recommended Comments to Applicant*

None at this time.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALIZA M THOMPSON
10/09/2015