CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205739Orig1s000

OTHER REVIEW(S)

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Regulatory Project Manager Overview

NDA:	205739
Drug:	Veltassa (Patiromer)
Class:	Potassium binders
Applicant:	Relypsa, Inc.
Indication:	Treatment of hyperkalemia
Date of submission:	October 21, 2014
PDUFA date:	October 21, 2015
Action date:	October 21, 2015

❖ **REVIEW TEAM**

- Office of New Drugs, Office of Drug Evaluation I, Division of Cardiovascular & Renal Products
  - Cross Discipline Team Leader (CDTL)
    - Aliza Thompson
  - Medical Reviewer
    - Shen Xiao
  - Pharmacology & Toxicology
    - William Link
  - Regulatory Health Project Manager
    - Sabry Soukehal
- Office of Pharmaceutical Quality
  - – CMC & Biopharmaceutics
    - Kasturi Srinivasachar (Application Technical Lead)
    - Raymond Frankewich (Drug Substance)
    - Mohan Sapru (Drug Product)
    - Elsbeth Chikhale (Biopharm)
    - Erika Pfeiler (microbiology)
    - Vipul Dholakia (Process)
- Office of Clinical Pharmacology
    - Ju-Ping Lai
- Office of Biostatistics, Division of Biometrics I
    - Fanhui Kong
- Office of Surveillance and Epidemiology
  - – DMEPA
    - Janine Stewart
  - DRISK
    - Leah Hart

❖ BACKGROUND

Veltassa for Oral Suspension is a new molecular entity developed by Relypsa Inc. for the treatment of hyperkalemia. It contains the drug substance Patiromer Sorbitex Calcium that belongs to the pharmacologic class of Potassium Binders. Patiromer, the (b) (4) of the drug substance, binds Potassium in the lumen of the colon resulting in its fecal excretion and lowering of serum Potassium levels.

The clinical development program for Veltassa comprised eight studies: three Phase 1 studies, four Phase 2 studies and one two-part Phase 3 study (RLY5016-301) conducted under a Special Protocol Assessment in which parts A and B served as one of two pivotal studies for marketing approval evaluation as indicated in the SPA Agreement Letter dated December 26, 2012. Subjects who participated in these eight clinical studies included patients with hyperkalemia, Chronic Kidney Disease, heart failure, diabetes, hypertension and/or patients who were receiving dialysis, and healthy volunteer subjects.

Phase 1 evaluation in healthy subjects consisted of two studies (RLY5016 -101 and RLY5016-102) which assessed the safety and pharmacology of Veltassa. A third Phase 2 pharmacology study (RLY5016-201) evaluated the pharmacodynamic effects and safety of the drug in hyperkalemic patients on hemodialysis.

Five clinical studies (RLY5016-301, RLY5016-205, RLY5016-103, RLY5016-202, and RLY5016-204) were conducted to assess the safety and efficacy of the drug. Efficacy was assessed in all studies using endpoints based on serum potassium levels.

The proposed doses are 8.4, 16.8, or 25.2 grams Patiromer once daily in packets for Oral suspension.

The NDA was given a standard review with a PDUFA date of October 21, 2015. The review of the application in general met all of the 21st century review guidelines through primary reviews.

User Fee

The user fee for this application was paid in full on October 15, 2014. User Fee ID 3014604.

Pediatric Review Committee (PeRC)

The applicant submitted a deferral request in Pediatrics. The PeRC meeting to discuss this application was held on September 23, 2015. The committee noted that the (b) (4) However, the PeRC agreed that studies could be delayed until the need for (b) (4) A deferral was granted with 2 postmarketing studies to be conducted (PMR 2980-1 and 2980-2).

Advisory Committee

There was no Advisory Committee meeting for this NDA because the clinical trial design and efficacy endpoints were deemed acceptable.

Trade name
The Applicant submitted the proposed name Veltassa to IND 75615 on June 19, 2014 and to the NDA on November 03, 2014. The name was approved on November 18, 2014. A grant letter was issued on November 25, 2014.

Facilities Inspection
The Office of Compliance provided an overall recommendation of acceptability for the manufacturing sites on August 10, 2015.

Division of Scientific Investigations
Three foreign clinical investigator inspections were conducted in support of NDA 205739. A site inspection also occurred at Relypsa, Inc. in California. No significant deficiencies were observed and no form 483 was issued. For more details please see the clinical inspection summary dated 6/22/15.

❖ REGULATORY TIMELINE

- NDA Received Date: October 21, 2014
- Filing Day 60: December 20, 2014
- Filing 74 Day Letter: December 24, 2014
- Mid-cycle Communication Meeting: April 02, 2015 (minutes dated May 01, 2015)
- Late-Cycle Meeting: June 29, 2015 (minutes dated July 27, 2015)
- Advisory Committee: N/A
- PDUFA Date: October 21, 2015

❖ REVIEWS

Below are the conclusions reached by the Veltassa team members, organized by role or discipline.

ODE I Memorandum
Dr. Unger provided a thorough synopsis of each disciplines review, (see full memo for details). He stated. He noted that, prior to approval and finalization of labeling, the applicant packaged their product in anticipation of a rapid launch. The memo indicates that although the cartons were properly labeled, the drug pouches inside the cartons carry a statement (b) (4) (b) (4) Per a October 20, 2015 teleconference with OPQ and the Division, the applicant has agreed to take corrective action by (b) (4) on all of the mislabeled packets prior to distribution. The applicant also agreed to correct the storage conditions with the next printing of the packets. Overall, Dr. Unger agrees with the review team's recommendation for approval.

Divisional Memorandum
Dr. Stockbridge indicated that he was in substantial agreement with the CDTL's conclusion. The memo indicates that the most commonly reported adverse effects (<10%) were GI symptoms that often resolved with continued treatment. The main safety issue is the potential for drug interactions through non-specific binding.

Cross-Discipline Team Leader (CDTL) Review
Dr. Thompson recommended approval pending resolution of outstanding CMC issues and agreement on labeling. Her review summarized each disciplines findings. She also provided a detailed regulatory history. She provided a thorough risk-benefit assessment.

Medical
Dr. Xiao provided a thorough clinical review and recommend that Veltassa be approved for the treatment of hyperkalemia in adults if the potential risk of drug-drug interactions can be adequately addressed

Biostatistics Review
Dr. Kong stated that The primary efficacy analysis in Part A of Study RLY5016-301 gave an overall mean change in serum potassium from Part A Baseline to Week 4 of -1.01 (with se of 0.031) mEq/L [95% CI: (-1.07, -0.95)] , that gave $p < 0.001$ in the comparison to zero. These results satisfied the agreement with FDA, so the primary efficacy results from Part A of the study were considered as pivotal. The estimated difference in median change from Part B baseline between placebo and Veltassa was 0.72 mEq/L with 95% CI (0.46, 0.99), and $p<0.001$ for between-group difference in mean ranks of change.
He concluded that these results provided adequate evidence to support the effectiveness of Veltassa in achieving a clinically meaningful reduction in serum potassium levels in subjects with hyperkalemia, (b) (4).

Clinical Pharmacology Review
Dr. Lai and the Office of Clinical Pharmacology recommended approval the following recommendations:
- Co-administration of Veltassa with other drugs should be avoided unless lack of binding to Veltassa has been demonstrated. The administration of Patiromer and other oral medical drugs should be spaced by 6 hours
- A QD regimen is recommended to help mitigate the drug interaction potential with Veltassa.
- Treatment should be initiated with a starting dose of 8.4 g/day and should be titrated based on response in increments of 8.4 g/day up to a maximum dose of 25.2 g/day.
- The titration interval should be at least one week or longer to maximize the effect that can be achieved with the dose.

Pharmacology & Toxicology Review
Dr. Link's review noted that pharmacology testing focused on the primary pharmacodynamic effect of the drug and that safety pharmacology studies were conducted to investigate the effects of RLY5016 on the cardiovascular, central nervous, respiratory and GI systems. RLY5016 was tested in rats and dogs. The maximum recommended human dose of RLY5016 is approximately (b) (4).
The requirement for carcinogenicity testing of RLY5016S was waived by the Division.
The reproductive and developmental toxicity of RLY5016S was evaluated in rat and rabbit studies. No significant effects were noted at any treatment level.
Dr. Link stated the preclinical toxicology program was thorough and well conducted. He agrees with the applicant's interpretations of the data and recommends approval.
For more information, please see Dr. Link's review.

Tertiary Pharmacology Review
Dr. Brown summarized the pharmacologists' review and agreed with his assessment. He also provided comments on labeling.

Office of Pharmaceutical Quality Review
An integrated summary was written for product quality. Approval is recommended from a quality standpoint.
From a Quality perspective, the drawback was the product's propensity to degrade upon storage to fluoride ion, which can potentially have toxic effects at the doses proposed. The Applicant has mitigated this problem by recommending long term storage at refrigeration temperature with shorter exposure to room temperature conditions. An (b) (4) has been assigned when stored refrigerated (2-8ºC).
There were several discussions throughout the review process regarding the elemental impurities in the drug substance and xanthan gum (b) (4).
From a Biopharmaceutics perspective, the assessment focused on (1) the evaluation of the information for the in vitro *Total Potassium Exchange Capacity (TPEC) assay* and (2) the in vitro bioequivalence information (*Equilibrium Binding and Kinetic Binding assays*).
The response of the TPEC assay was evaluated and deemed acceptable. The reviewer concluded that formulation bridging was not required to support this NDA, and that in vitro bioequivalence tests were appropriate.
From a microbiology perspective, the tests and proposed acceptance criteria for microbial burden are adequate.
From a manufacturing process standpoint, the review led to no specific risks and concluded that it was adequately developed and controlled for consistent manufacture of the drug product.

❖ CONSULTS

Office of Surveillance and Epidemiology
DMEPA
Dr. Stewart reviewed the container labels, carton labeling, Prescribing Information, (b) (4) (b) (4) For Use. A risk assessment was performed and concluded that the carton labeling, PI and (b) (4) were acceptable. Full details on recommendations can be found in the review dated August 27, 2015. Final agreed-upon cartons were submitted October 16, 2015.

DRISK
Dr. Hart evaluated the need for a risk evaluation and mitigation strategy (REMS). She concluded risk mitigation measures beyond labeling are not necessary as the benefit-risk profile for Veltassa was acceptable. See full review dated October 21, 2015 for details.

Office of Medical Policy, Division of Medical Policy Programs
Ms. Dowdy did a combined review with Dr. Shah evaluating the Medication Guide and (b) (4) See full review dated October 08, 2015 for details. They concluded that the document is acceptable pending proposed corrections.

Office of Prescription Drug Promotions, Division of Professional Drug Promotion
Dr. Shah provided comments on the draft Package Insert. See full review dated October 08, 2015 for details.

❖ LABELING

Labeling discussions occurred with the applicant. The final agreed-upon labeling (that excluded the Instructions for use) was attached to the approval letter.

❖ CONCLUSION

The review team recommended approval.

An approval letter was created and signed by Dr. Unger on October 21, 2015.

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/s/

SABRY SOUKEHAL
10/23/2015

MEMORANDUM

REVIEW OF LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 22, 2015
Requesting Office or Division:	Division of Cardiovascular and Renal Products (DCRP)
Application Type and Number:	NDA 205739
Product Name and Strength:	Veltassa (patiromer) For Oral Suspension 8.4 g Physician Sample
Submission Date:	September 4, 2015
Applicant/Sponsor Name:	Relypsa, Inc.
OSE RCM #:	2014-2292-2
DMEPA Primary Reviewer:	Janine Stewart, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMO

The Division of Cardiovascular and Renal Products (DCRP) requested that we review the proposed container label and carton labeling (Appendix A) for an 8.4 g physician sample to determine if they are acceptable from a medication error perspective. Relypsa, Inc. has proposed to add this new 8.4 g physician sample to the Veltassa product line after the ~~container labels and carton l~~abeling for the 8.4 g, 16.8 g, and 25.2 g commercial configurations

[1] Stewart J. Label and Labeling Memo for Veltassa (NDA205739). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 JUN 1. 7 p. OSE RCM No.: 2014-2292-1.

[2] Stewart J. Label and Labeling Review for Veltassa (NDA205739). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 FEB 13. 28 p. OSE RCM No.: 2014-2292.

[3] Stewart J. Label and Labeling Review for Veltassa (NDA205739). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 AUG 26. 14 p. OSE RCM No.: 2015-1176.

were reviewed and found acceptable in a label and labeling memorandum subsequent to the initial review and in a review of revised labels corresponding to the streamlined Veltassa product line.[1,2,3]

2 CONCLUSION & RECOMMENDATIONS

The newly proposed physician sample container label and carton labeling are unacceptable from a medication error perspective. Representing the 8.4 g professional sample with a color that is different from the 8.4 g commercial package can cause product selection errors. The proposed teal color could be confused with the 16.8 g strength. Additionally, the use of two different colors for the same strength could be perceived as a difference in formulation of the physician sample versus the commercial package. Further, the "Physician Sample; Not for Sale" statement can be relocated for improved prominence. We recommend the following changes to the container label and carton labeling be implemented prior to approval of this NDA:

1. Revise the color scheme of the 8.4 g physician sample to use the same purple color scheme that is consistent with the 8.4 g commercial packaging.

2. Relocate the "Physician Sample; Not for Sale" statement to the top of the principal display panel of the container label and the carton labeling for increased prominence.

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/s/

JANINE A STEWART
10/22/2015

CHI-MING TU
10/22/2015

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	October 07, 2015
To:	Norman Stockbridge, MD, PhD Director **Division of Cardiovascular and Renal Products (DCRP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Karen Dowdy, RN, BSN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Puja Shah, Pharm.D. Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and (b) (4)
Drug Name (established name):	VELTASSA (patiromer)
Dosage Form and Route:	for oral suspension
Application Type/Number:	NDA 205739
Applicant:	Relypsa, Inc.

1 INTRODUCTION

On October 21, 2014, Relypsa, Inc. submitted for the Agency's review an original New Drug Application (NDA) 205739 for VELTASSA (patiromer) for oral suspension with the proposed indication for the treatment of hyperkalemia.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to the requests by the Division of Cardiovascular and Renal Products (DCRP) on January 29, 2015, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) (b) (4) for VELTASSA (patiromer) for oral suspension. On May 20, 2015 the Applicant submitted revised labeling including a Medication Guide (MG) (b) (4) in response to the Agency's Mid-Cycle Communication dated May 01, 2015.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the (b) (4) was completed on August 26, 2015.

2 MATERIAL REVIEWED

- Draft VELTASSA (patiromer) for oral suspension MG received on August 12, 2015 and received by DMPP on August 12, 2015.
- Draft VELTASSA (patiromer) for oral suspension MG received on August 12, 2015, and received by OPDP on October 4, 2015.
- Draft VELTASSA (patiromer) for oral suspension (b) (4) received on August 10, 2015 and received by DMPP on August 11, 2015.
- Draft VELTASSA (patiromer) for oral suspension (b) (4) received on August 10, 2015, and received by OPDP on October 4, 2015.
- Draft VELTASSA (patiromer) for oral suspension Prescribing Information (PI) received on May 20, 2015, revised by the Review Division throughout the review cycle, and received by DMPP on October 01, 2015.
- Draft VELTASSA (patiromer) for oral suspension Prescribing Information (PI) received on May 20, 2015, revised by the Review Division throughout the review cycle, and received by OPDP on September 30, 2015.
- Division of Medication Error, Prevention, and Analysis (DMEPA) Label and Labeling Review for Veltassa (patiromer) For Oral Suspension dated August 26, 2015.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG (b) (4) the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Arial font, size 10 and the (b) (4) using the Arial font, size 11.

In our collaborative review of the MG (b) (4) we have:

- simplified wording and clarified concepts where possible
- ensured that the MG (b) (4) are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG (b) (4) are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG (b) (4) meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- The enclosed (b) (4) review comments are collaborative DMPP and DMEPA.

4 CONCLUSIONS

The MG (b) (4) are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG (b) (4) is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG (b) (4).

Please let us know if you have any questions.

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/s/

SHAWNA L HUTCHINS
10/07/2015

PUJA J SHAH
10/08/2015

LASHAWN M GRIFFITHS
10/08/2015

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: October 8, 2015

To: Sabry Soukehal
Regulatory Project Manager
Division of Cardiovascular and Renal Products (DCRP)

From: Puja Shah, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 205739
Veltassa (patiromer) for oral suspension

As requested in DCRP's consult dated January 2, 2015, OPDP has reviewed the draft Package Insert, Medication Guide, (b) (4) for Veltassa (patiromer) for oral suspension. OPDP's comments are based on the substantially complete version of the labeling titled "NDA 205739 draft label received from Aliza on 9.29.15.docx" which was emailed by DCRP (Sabry Soukehal) on September 30, 2015.

Package Insert (PI)

Our comments on the draft PI are included directly on the attached copy of the labeling.

Medication Guide (MG) (b) (4)

Our review of the MG (b) (4) was conducted jointly with DMPP and filed under separate cover on October 8, 2015.

OPDP appreciates the opportunity to provide comments on these materials. If you have any questions or concerns, please contact Puja Shah at 240-402-5040 or puja.shah@fda.hhs.gov

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/s/

PUJA J SHAH
10/08/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	August 26, 2015
Requesting Office or Division:	Division of Cardiovascular and Renal Products (DCRP)
Application Type and Number:	NDA 205739
Product Name and Strength:	Veltassa (patiromer) For Oral Suspension 8.4 g, 16.8 g, and 25.2 g
Product Type:	Single Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Relypsa, Inc.
Submission Date:	July 20, 2015 and August 10 , 2015
OSE RCM #:	2015-1176
DMEPA Primary Reviewer:	Janine Stewart, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

As part of the new molecular entity NDA review for Veltassa (patiromer) for Oral Suspension, this review evaluates the proposed revised container labels, carton labeling, Prescribing Information (PI), (b) (4) for areas of vulnerability that can lead to medication errors in response to a request from the Division of Cardiovascular & Renal Products (DCRP).

Following the Late Cycle Meeting on June 29, 2015, the Applicant agreed with FDA's labeling recommendations which included the following:

- Change from (b) (4) to once daily (QD) dosing.
- (b) (4)
- (b) (4)

These changes are reflected in proposed revisions to the PI (b) (4). In addition, the change to once daily dosing is reflected in proposed carton labeling with a revised net quantity of 30 packets. Further, the change to once daily dosing with a 13 starting dose of 8.4 g and a maximum daily dose of 25.2 g per day allowed for a streamlined the product line to supply the proposed dosage strengths of 8.4 g, 16.8 g, and 25.2 g (b) (4)

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C- N/A
ISMP Newsletters	D- N/A
FDA Adverse Event Reporting System (FAERS)*	E- N/A
Other	F- N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA performed a risk assessment of the revised PI, the revised container labels and carton labeling and the revised (b) (4) to identify deficiencies that may lead to medication errors and areas for improvement. We note the guidance for dose titration that is provided in the Dosage and Administration sections of the *Highlights of Prescribing Information* and in the *Full Prescribing Information* can be clarified for safe use of the product and for consistency between the sections. We also note (b) (4) can be improved for readability. Our assessment of the revised container labels and carton labeling found them to be acceptable from a medication error perspective. However, the intended use of the 8.4 g - 4 packet carton configuration is unclear.
We have provided recommendations to promote the safe use of Veltassa in Section 4.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed container labels and carton labeling ae acceptable. However, the PI (b) (4) can be improved to increase clarity, readability, and the prominence of important information to promote the safe use of this product.

4.1 RECOMMENDATIONS FOR THE DIVISION

Based on this review, we have recommendations for revisions to the Full Prescribing Information (b) (4) for review and consideration by DCRP.

Prescribing Information (PI)

1. Revise the Dosage and Administration section of the Highlights of Prescribing Information to include the recommended dosing and titration instructions provided in Section 2.2 of the Full Prescribing Information for consistency.

2. Clarify the titration interval described in Section 2.2 of the Full PI. As currently proposed, “the dose may be increased or decreased by 8.4 grams daily.” and “dose can be uptitrated at 1-week or longer intervals.” It is unclear whether the dose of Veltassa can be up titrated from 8.4 gram on day 1 to 16.8 grams on day 2, or the dose should not be up titrated to 16.8 gram until day 8.

3. Revise the PI to include instructions for titrating from a higher dose to a lower dose and clarify the titration interval in terms of the number of days instead of weeks for greater clarity.

4. (b) (4)

(b) (4)

1. (b) (4)

4.2 RECOMMENDATIONS FOR THE APPLICANT

We recommend the following be implemented prior to approval of this NDA.

Carton Labeling- 8.4g

1. Clarify the intended use for the 4-count packaging configuration of the 8.4 g strength.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Veltassa that Relypsa, Inc. submitted on July 20, 2015.

Table 2. Relevant Product Information for Veltassa	
Initial Approval Date	N/A
Active Ingredient	patiromer
Indication	Veltassa is a potassium binder indicated for the treatment of hyperkalemia.
Route of Administration	Oral
Dosage Form	Oral suspension
Strength	8.4 g, 16.8 g, and 25.2 g
Dose and Frequency	Starting dose is 8.4 g once daily with food. Titrate dose to within desired serum potassium range after one week or longer by increments of 8.4 g. Maximum once daily dose is 25.2 g with food.
How Supplied	Powder for oral suspension packaged in single-use packets, which is supplied in cartons of 4 or 30 single-use packets.
Storage	Veltassa should be stored in the refrigerator at 2°C to 8°C (36°F to 46°F). (b) (4) If stored at room temperature (b) (4) Veltassa must be used within 3 months of being taken out of the refrigerator. For either storage condition, do not use Veltassa after the expiration date printed on the packet.
Container Closure	(b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On August 10, 2015, we searched the L: drive and AIMS using the terms, Veltassa to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified one previous review[1] and we confirmed that our previous recommendations were implemented.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[2] along with postmarket medication error data, we reviewed the following Veltassa labels and labeling submitted by Relypsa, Inc.

- Container label (submitted August 10, 2015)
- Carton labeling (submitted August 10, 2015)
- (b) (4)
- Full Prescribing Information (submitted July 20, 2015)- no image

[1] Stewart, J. Label and Labeling Review for Veltassa (patiromer) NDA 205739. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 FEB 12. RCM No.: 2014-2292.

[2] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

JANINE A STEWART
08/26/2015

CHI-MING TU
08/27/2015

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: June 22, 2015

TO: Aliza Thompson, Team Leader
Shen Xiao, Medical Officer
Sabry Soukehal, Regulatory Health Project Manager
Division of Cardio-Renal Drug Products

FROM: Sharon K. Gershon, Pharm.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Susan Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 205739

APPLICANT: Relypsa, Inc.

DRUG: VELTASSA® (patiromer sorbitex calcium) (RLY5016S)

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority

PROTOCOLS:

1. **Study RLY5016-205:** A Multicenter, Randomized, Open-Label, Dose Ranging Study to Evaluate the Efficacy and Safety of RLY5016 in the Treatment of Hyperkalemia in Patients with Hypertension and Diabetic Nephropathy Receiving ACEI and/or ARB Drugs, with or without Spironolactone (AMETHYST-DN)

2. **Study RLY5016-301:** A Two-Part, Single-Blind, Phase 3 Study Evaluating the Efficacy and Safety of Patiromer for the Treatment of Hyperkalemia

INDICATION: Treatment of hyperkalemia

CONSULTATION REQUEST DATE: December 16, 2014

INSPECTION SUMMARY GOAL DATE: June 21, 2015

PDUFA DATE: October 21, 2015

ACTION GOAL DATE: June 21, 2015

I. BACKGROUND:

Relypsa, Inc. submits NDA 205739, for patiromer sorbitex calcium (RLY5016) for oral suspension, with an indication for the treatment of hyperkalemia. Two studies, RLY5016-205, a dose-ranging study and RLY5016-301, a two-part Phase III study, provide primary support for the efficacy and safety of RLY5016 for this indication.

The drug substance, patiromer sorbitex calcium (referred to as RLY5016), is a new chemical entity belonging to the pharmacologic class of Potassium Binders. Patiromer is a non-absorbed cation-exchange polymer that binds potassium in the lumen of the colon and increases fecal potassium excretion, leading to removal of potassium from the body and lowering of serum potassium levels.

Study RLY5016-301: A Two-Part, Single-Blind, Phase 3 Study Evaluating the Efficacy and Safety of Patiromer for the Treatment of Hyperkalemia

RLY5016-301 was a single-blind study in subjects with chronic kidney disease (CKD) (with estimated glomerular filtration rate [eGFR] $\geq$ 15 mL/min/1.73m^2 and $<$ 60 mL/min/1.73 m^2) who were receiving a stable dose of at least one renin angiotensin aldosterone system inhibitor (RAASi). At the beginning of the study, subjects were required to be hyperkalemic as evidenced by a screening serum potassium that was 5.1 to $<$ 6.5 mEq/L (average of two values assessed by the local laboratory). The study consisted of two sequential parts: Part A was an assessment of 4 weeks of dosing with RLY5016 for Oral Suspension in the treatment of hyperkalemia; Part B was a randomized, placebo-controlled, 8-week assessment of the

withdrawal of RLY5016 for Oral Suspension conducted in those subjects with a baseline serum potassium (central laboratory) at the beginning of Part A ≥ 5.5 mEq/L who responded to the 4 weeks of treatment with RLY5016 for Oral Suspension during Part A.

Type of Population: men and women, 18 – 80 years of age, hypokalemic (serum potassium between 5.1 to < 6.5 mEq/L), with CKD defined as an estimated glomerular filtration rate (e-GFR) ≥ 15 mL/min/1.73 m^2, and receiving a stable dose of at least one renin angiotensin aldosterone system inhibitor (RAASi) for at least 28 days prior to screening.

For Part A subjects who met eligibility criteria (including screening serum potassium of 5.1 to < 6.5 mEq/L) were assigned to one of two starting dose groups:

- Dose Group 1 – Subjects with a screening serum potassium (local laboratory) of 5.1 to < 5.5 mEq/L were assigned to a starting RLY5016 for Oral Suspension dose of 8.4 g/day patiromer (administered as 4.2 g twice daily [BID]).

- Dose Group 2 – Subjects with a screening serum potassium (local laboratory) of 5.5 to < 6.5 mEq/L were assigned to a starting RLY5016 for Oral Suspension dose of 16.8 g/day patiromer (administered as 8.4 g BID).

During Part A, the RLY5016 for Oral Suspension dose was titrated, if needed, continuing through weekly visits (Part A Week 1, 2, and 3) to the end of 4 weeks of treatment with the aim of achieving serum potassium in a target range of 3.8 to < 5.1 mEq/L.

The primary efficacy endpoint for Part A was the change in serum potassium (central laboratory) from Part A baseline to the Part A Week 4 visit. Changes in serum potassium from baseline to other scheduled visits during Part A were also summarized but not considered formal endpoints. The secondary efficacy endpoint for Part A was the proportion of subjects with a centrally measured serum potassium level that was in the Part A target range of 3.8 to < 5.1 mEq/L after 4 weeks of treatment with RLY5016 for Oral Suspension.

Part B was a randomized, placebo-controlled, 8-week assessment of the withdrawal of RLY5016 for Oral Suspension. Subjects with a baseline serum potassium ≥ 5.5 mEq/L (central laboratory) at the beginning of Part A were entered into Part B of the study if they had responded to the 4 weeks of treatment with RLY5016S during Part A, defined as completing Part A and satisfying other requirements at the Part A Week 4 visit: (1) serum potassium (local laboratory) in the target range for Part A (3.8 to < 5.1 mEq/L), (2) receiving a RAASi and (3) receiving RLY5016 for Oral Suspension at a dose of 8.4 to 50.4 g/day patiromer.

Subjects eligible for Part B were randomized equally to either (1) continue RLY5016 for Oral Suspension at the same daily dose as administered at the time of the Part A Week 4 visit or (2) withdraw (i.e., discontinue) RLY5016 for Oral Suspension and receive placebo for an additional 8 weeks.

The primary efficacy endpoint for Part B was the change from Part B baseline (central laboratory) serum potassium to serum potassium at either:

• the Part B Week 4 visit, if the subject's serum potassium (local laboratory) remained ≥ 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 (local laboratory) was < 3.8 mEq/L or ≥ 5.5 mEq/L.

Study RLY5015-301 enrolled 243 subjects in Part A of the study and 108 subjects in Part B of the study.

Study RLY5016-205: A Multicenter, Randomized, Open-Label, Dose Ranging Study to Evaluate the Efficacy and Safety of RLY5016 in the Treatment of Hyperkalemia in Patients with Hypertension and Diabetic Nephropathy Receiving ACEI and/or ARB Drugs, with or without Spironolactone

Study RLY5016-205 was a Phase 2, multicenter, randomized, open-label, dose-ranging study to determine the optimal starting dose, efficacy and safety of RLY5016 for Oral Suspension in treating hyperkalemia in hypertensive subjects with nephropathy due to Type 2 diabetes mellitus (T2DM) receiving ACEI and/or ARB drugs, with or without spironolactone.

Type of Population: Men and women ages 30 to 80 years old, diagnosed with type 2 diabetes mellitus (T2DM) after 30 years of age and with chronic kidney disease (CKD) defined as GFR 15 to < 60 mL/min/1.73 m^2.

Study RLY50015-205 had two treatment periods: a Treatment Initiation Period (TIP) that lasted 8 weeks, followed by a Long-term Maintenance Period for an additional 44 weeks.

The original protocol was designed to enroll non-hyperkalemic subjects who could potentially benefit from initiation or optimization of renin-angiotensin-aldosterone system (RAAS) therapy, and would be eligible for treatment with RLY5016 for Oral Suspension if hyperkalemia developed during a run-in period. However, as the study progressed, it became apparent that many subjects who met all other eligibility criteria also already had hyperkalemia, and the protocol was amended to allow these patients to be enrolled directly into the study (i.e., without the RAAS run-in period). Amendment 1 divided the eligible population into non-hyperkalemic subjects and subjects with hyperkalemia, providing different paths to study drug treatment initiation.

Subjects from all cohorts were assigned to one of two strata according to their baseline serum potassium level and initiated RLY5016 for Oral Suspension treatment at randomly assigned starting doses in a 1:1:1 ratio as follows:

Stratum: 1 (serum potassium > 5.0 to 5.5 mEq/L)		**2 (serum potassium > 5.5 to 6.0 mEq/L**	
10 g/day	8.4 g/day (anion form)	20 g/day	16.8 g/day (anion form)
20 g/day	16.8 g/day (anion form)	30 g/day	25.2 g/day (anion form)
30 g/day	25.2 g/day (anion form)	40 g/day	33.6 g/day (anion form)

Study RLY5016-205 randomized 306 subjects at 48 sites in 5 countries: Croatia, Georgia, Hungary, Serbia, and Slovenia.

Reasons for Site Selection: Sites chosen for inspection had high enrollment. In addition:

- Site 1310 (Giorgadze) had high treatment effect size for primary efficacy in Part A of trial RLY5016-301.
- Site 308 (Mamatsashvili) had no Serious Adverse Events and a low number of Adverse Events reported relative to the study average in trial RLY5016-205.
- Site 303 (Shaburishvili) had a high favorable treatment effect size in trial RLY5016-205.
- Site 1305 (Shaburishvili) had a high favorable treatment effect size in Part A and B of trial RLY5016-301.

II. Results

Name of CI/Location	Protocol #, Site #, and # of Subjects	Inspection Dates	Final Classification
Elene Giorgadze Tbilisi, Georgia	RLY 5016-301 Site 1310 11 subjects	March 30 – 31, 2015	NAI
Merab Mamatsashvili Tbilisi, Georgia	RLY 5016-205 Site 308 32 subjects	April 1 – 3, 2015	NAI
Tamaz Shaburishvili Tbilisi, Georgia	RLY5016-205 Site 303 34 subjects RLY5016-301 Site 1305 9 subjects	March 23 – 27, 2015	NAI
Relypsa Inc. Redwood City, CA	RLY5016-205 RLY5016-301	Feb 23 – 27, 2015	NAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. **Elene Giorgadze (Site #1310)**
2/6 Ljubljana Street
Tbilisi, Georgia

a. What was inspected: The inspection audited protocol RLY5016-301. Dr. Giorgadze has (b) (4) IND studies listed in the CDER database and no prior inspections. This site was chosen for inspection because of high enrollment and high treatment effect size favoring active drug in Part A of Study 301.

This site screened fourteen subjects and enrolled eleven subjects. A total of seven subjects completed the study. Four subjects withdrew early from the study.

The inspection reviewed source documents and case report forms for the eleven randomized subjects and the three subjects who were screen failures. The inspection also reviewed IRB/Ethics Committee correspondences, subject assessments and medical notes, monitoring logs, drug accountability records, protocol deviations, and compared the source records to data listings for all data provided with the assignment.

b. General observations/commentary: Relypsa contracted with Worldwide Clinical Trials in Georgia to monitor the study. The inspection observed that there was one site initiation visit in February 2013, and that monitoring visits occurred monthly through July 2013. The final close-out visit occurred on December 24, 2014.

The inspection found that the subjects met inclusion and exclusion criteria and that the informed consent documents were signed before screening. The source documents corroborated with the data listings. There were no deficiencies.

c. Assessment of data integrity: No significant deficiencies were observed, and no Form FDA 483 was issued. The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

2. **Merab Mamatsashvili (Site #308)**
16 Kavtaradze Street
Tbilisi, Georgia

a. **What was inspected:** The inspection audited protocol RLY5016-205. Dr. Mamatsashvili has (b) (4) IND studies listed in the CDER database, and no prior FDA inspections. This site was chosen for inspection because there were no Serious Adverse Events (SAEs) reported and a low number of AEs reported relative to the study average.

The site screened 44 subjects and enrolled 32 subjects. A total of 30 subjects completed the study. There were twelve screen failures and two early withdrawals – Subjects 30815 and 30823.

The inspection reviewed the following items: authority and administration of the study (verification of central and local laboratories, review of financial disclosure statements,

protocol training, site signature and delegation of responsibility logs); sponsor monitoring (monitoring site visit log and follow-up correspondence letters from the monitor); Ethics Committee approvals of the protocol; regulatory binders (including various correspondences from the sponsor); organization of subject binders; written medical notes and laboratory results; drug accountability records; and detailed study record review for thirteen subjects that included adherence to the protocol and corroboration of source documents with data tables submitted with the assignment.

b. General observations/commentary: Relypsa contracted with Worldwide Clinical Trials in Georgia to monitor the study. The Site Visit Log showed one site initiation visit for training on May 24, 2011, twenty-one site monitoring visits, two sponsor audits, and a final close-out visit on December 4, 2013.

For the thirteen study records reviewed, the inspection verified subject eligibility at screening, and ensured that subjects followed the Schedule of Events for the Screening Period (up to ten days), Run–In (up to four weeks), Treatment Initiation Period (eight weeks duration), Long-Term Maintenance Period (44 weeks), and Follow Up Period (three weeks).

The field investigators reported that subject records (source files) were organized by visit dates, and contained all the relevant medical information for the visit along with written notes by the Sub-investigator verifying compliance with the protocol.

The study reported one Serious Adverse Event (SAE) that resulted in a subject death on (b) (6) due to a stroke (Subject 30815). The subject was removed from the study on (b) (6). Subject 30823 was the only other subject who voluntarily withdrew participation from the study.

For records reviewed, the inspection found that subjects met eligibility criteria; that informed consent documents were signed prior to screening; that local and central laboratory test results, vital signs, and concomitant medications were well-documented; that protocol deviations, adverse events and serious adverse events were documented and reported to the Ethics Committee and sponsor within the required timeframes. The primary and secondary efficacy variables related to serum potassium and clinical chemistry values of urine albumen and vital signs at Weeks 4 and 8. The inspection found that all endpoints were verifiable and no deficiencies were found. Results of review of drug accountability records were acceptable with no major deficiencies. Review of the Patient Screening and Enrollment log found no discrepancies.

c. Assessment of data integrity: No significant deficiencies were observed and no Form FDA 483 was issued. The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

3. **Tamaz Shaburishvili (Site 303 for Study 205; Site 1305 for Study 301)**
18/20 Ljubljana Street
Tbilisi, Georgia

a. What was inspected: The inspection audited protocols RLY5016-205 and RLY5016-301. Dr. Shaburishvili has (b) (4) IND studies listed in the CDER database. (b) (4) This site was chosen for inspection because of high enrollment and high treatment effect size favoring treatment arm in Study 205, and high treatment effect size in Parts A and B of Study 301.

The enrollment log for Study RLY5016-205 showed that 41 subjects were screened, 34 subjects enrolled, and 28 subjects completed the study. Six subjects withdrew early; there were six screen failures, and one enrollment failure.

For Study RLY5016-301 the enrollment log showed that eleven subjects were screened. For Part A, nine subjects were enrolled, and nine subjects completed the study. For Part B, nine subjects were enrolled, and four subjects completed the study. For Part B Subjects 130506, 130510, and 130511 were terminated early, and Subjects 130508 and 130509 were screen failures.

For both studies the inspection reviewed the following items: authority and administration of both studies (verification of central and local laboratories, review of financial disclosure statements, protocol training, site signature, and delegation of responsibility logs); sponsor monitoring (monitoring site visit log and follow-up correspondence letters from the monitor); Ethics Committee approvals of the protocol; regulatory binders (including various correspondences from the sponsor); organization of subject binders; written medical notes and laboratory results; drug accountability records; and detailed study record review for fourteen subjects in Study RLY5016-205 and seven subjects in Study RLY5016-301, which included adherence to the protocol and corroboration of source documents with data tables submitted with the assignment.

b. General observations/commentary: Relypsa contracted with Worldwide Clinical Trials in Georgia to monitor both studies. For Study RLY5016-205, the Site Visit Log identified three pre-study and initiation visits, twenty-five monitoring visits, and a close-out visit on November 27, 2013. For Study RLY5016-301, there was one site initiation visit on February 15, 2013, six monitoring visits, two sponsor audits, and a final close-out visit on October 22, 2013.

Review of the correspondence file for both studies revealed that the monitors documented their findings in a follow-up letter to the site that the local Ethics Committee was responsible for oversight of the studies, and the site adhered to Good Clinical Practice guidelines.

Regulatory binders, study information and drug accountability records were organized and well documented. The inspection observed that all files contained relevant medical

information for the visit with written notes by the investigator verifying compliance with the protocol.

For Study RLY5016-205 there were six SAEs including three deaths: 1) Subject 30323 had sudden death with failure to resuscitate, 2) Subject 30324 had endotoxic shock after surgery of a lower limb due to diabetic angiopathy, and 3) Subject 30329 had a stroke. Other SAEs included: Subject 30317 had hospitalization for peripheral revascularization due to diabetic angiopathy, Subject 30305 had an appendectomy, and Subject 30334 had heart failure.

For Study RLY5016-205 the primary and secondary efficacy endpoints were verifiable. Subjects signed the Informed Consent Document prior to screening. The only objectionable finding was that the initial drug accountability records did not have a column to document the Lot numbers for the test articles dispensed under IVRS. Therefore, it was not clear from the accountability records alone that subjects were administered the prescribed IVRS medications. The sponsor recognized the problem during the study, and corrected the forms so that Lot Numbers could be documented.

The above finding is unlikely to significantly impact the reliability of the data for this study from this site.

c. **Assessment of data integrity:** No significant deficiencies were observed for either study, and no Form FDA 483 was issued. The studies appear to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

4. Relypsa, Inc.
100 Cardinal Way
Redwood City, CA 94063

a. What was inspected: The focus of the inspection was on the three sites where BIMO inspections occurred and the two studies that supported efficacy: For each study the following was reviewed:

- FDA 1572s and financial disclosures
- Organizational structure
- Contracts for transfer of regulatory obligations to Contract Research Organizations (CROs).
- Audit certificates and audit plans. The inspection did not review the results of those audits.
- Contract with Worldwide Clinical Trials (WCT), the main CRO for both studies.
- Investigator brochures (IB). Comparison of IB to the protocol, consent forms, and reported adverse events.
- Monitoring plans, list of monitors.
- Monitoring reports for Sites 303, 308, 503, 505, 517, and 607 in RLY5016-205
- Monitoring reports for Sites 1104, 1303, 1305, 2105, and 3102 in RLY5016-301.

- Electronic Data Capture (EDC) systems and IWRS (Interactive Web Response System).
- Queries run as part of data cleanup.
- Investigational product and placebo shipment logs, temperature logs, drug accountability records and labeling.

b. General observations/commentary: Relypsa's management for both studies was similar. Each study used a different provider for their Electronic Data Capture systems, IVRS and central laboratories. All other contractors were the same.

Worldwide Clinical Trials (WCT) was the primary CRO who identified potential sites, and provided monitoring. Relypsa approved sites after a careful review of the CV, a feasibility questionnaire and a Pre-Study Site Visit (PSSV).

For RLY5016-205, 53 sites were activated in the Interactive Voice Response System (IVRS). Of those 53, 48 sites screened at least one subject, and 43 sites enrolled at least one subject.

For Study RLY5016-301, 78 sites were activated in the IVRS, 71 sites screened subjects, and 59 sites enrolled subjects.

No issues were identified in the review of the investigator brochure. There were two monitoring plans – one covered on-site monitoring activities, and the other covered medical monitoring. The medical monitoring logs for each study captured incidents such as serious adverse events, deaths and protocol deviations appropriately

Although no sites were terminated during either trial, Sites 503 and 505 in Study RLY5016-205 had enrollment suspended due to untimely recordkeeping problems at the investigational site. As part of remedial action at those sites, the monitor was removed and replaced. Site 503 resumed enrollment after corrections were made, and Site 505 remained in the trial but did not enroll any further subjects.

No issues were identified relating to investigational product and labeling. Used containers and unused medications were destroyed by WCT.

All deaths during the studies were reviewed by a safety board, as stipulated in the Charter. Subjects who did not meet protocol requirements were excluded from the per protocol analysis.

.

There was no evidence for under-reporting of adverse events and there were no issues with the primary efficacy variable.

c. Assessment of data integrity: No Form FDA 483 was issued. The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Three foreign clinical investigator site inspections and a Sponsor inspection were conducted in support of NDA 205739. No regulatory violations were found during the clinical investigator inspections and no violations were observed during the sponsor site inspection. All inspections were classified as NAI. Therefore, the data from this study may be considered reliable.

{See appended electronic signature page}

Sharon Gershon, Pharm.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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/s/

SHARON K GERSHON
06/22/2015

SUSAN D THOMPSON
06/22/2015

KASSA AYALEW
06/22/2015

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	June 1, 2015
Requesting Office or Division:	Division of Cardiovascular and Renal Products (DCRP)
Application Type and Number:	NDA 205739
Product Name and Strength:	Veltassa (patiromer) For Oral Suspension (b) (4) 8.4 g, (b) (4) 16.8 g, (b) (4) and 25.2 g
Submission Date:	May 15, 2015
Applicant/Sponsor Name:	Relypsa, Inc.
OSE RCM #:	2014-2292-1
DMEPA Primary Reviewer:	Janine Stewart, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMO

The Division of Cardiovascular and Renal Products (DCRP) requested that we review the revised container labels and carton labeling (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[1]

2 CONCLUSIONS

The revised container labels and carton labeling are acceptable from a medication error perspective.

[1] Stewart J. Label and Labeling Review for Veltassa (NDA205739). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 FEB 13. 28 p. OSE RCM No.: 2014-2292.

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JANINE A STEWART
06/01/2015

CHI-MING TU
06/01/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	February 12, 2015
Requesting Office or Division:	Division of Cardiovascular and Renal Products (DCRP)
Application Type and Number:	NDA 205739
Product Name and Strength:	Veltassa (patiromer) For Oral Suspension (b) (4) 8.4 g, (b) (4) 16.8 g, (b) (4) and 25.2 g
Product Type:	Single Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Relypsa, Inc.
Submission Date:	October 21, 2014 and December 9, 2014
OSE RCM #:	2014-2292
DMEPA Primary Reviewer:	Janine Stewart, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

As part of the new molecular entity NDA review for Veltassa (patiromer) for Oral Suspension, this review evaluates the proposed container labels, carton labeling, and Prescribing Information for areas of vulnerability that can lead to medication errors in response to a request from the Division of Cardiovascular & Renal Products (DCRP).

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B- N/A
Previous DMEPA Reviews	C- N/A
Human Factors Study	D- N/A
ISMP Newsletters	E- N/A
Other	F- N/A
Labels and Labeling	G
Full Prescribing Information	H

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA performed a risk assessment of the proposed Prescribing Information, the container labels and carton labeling to identify deficiencies that may lead to medication errors and areas for improvement. We note the use of trailing zeroes on the container labels and carton labeling for Veltassa (b) (4) in areas of the Prescribing Information. We also note the proprietary name presentation can be revised for improved readability. In addition, we note the preparation instructions provided on the container label can be more consistent with the preparation instructions provided in the Prescribing Information. After further review of the Prescribing Information, we find that the active ingredient is not defined in the statement of equivalence and in the product description section. Thus, we provide recommendations to mitigate confusion and promote the safe use of this product in Section 4.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling can be improved to increase clarity, readability, and the prominence of important information to promote the safe use of this product.

4.1 RECOMMENDATIONS FOR THE DIVISION

Based on this review, we have made revisions to the Full Prescribing Information (See Appendix H) and have provided a detailed summary below for review and consideration by DCRP.

Prescribing Information (PI)

1. Trailing zero [redacted] (b) (4)) is used in the Dosage Forms and Strength section of the Highlights of PI and in Sections 2, 3, 11 and 16 of the full PI. Remove trailing zeros where they appear throughout the PI to avoid 10-fold errors of measurement.

2. Add the recommended route of administration (i.e. oral) to the *General Dosing Information* in Section 2.1.

3. [redacted] (b) (4)

4. [redacted] (b) (4)

5. In Section 11 of the PI, we note the active ingredient is not defined. We defer to CMC for the correct nomenclature for the active ingredient.

4.2 RECOMMENDATIONS FOR RELYPSA, INC.

DMEPA recommends the following be implemented prior to approval of this NDA:

General Comments (Container Labels and Carton Labeling)

1. Revise the presentation of the proprietary name from all upper case (i.e. VELTASSA) to title case (i.e. Veltassa) to improve the readability of the name.

2. Ensure that the established name is expressed in a font size that is at least half the size of the font used in the proprietary name in accordance with 21 CFR 201.10(g)(2).

3. Remove the trailing zero in the (b) (4) strength expression ((b) (4)) on all labels and labeling panels to avoid a ten-fold misinterpretation.

4. Revise the statement "(b) (4) " to read "Usual Dosage: see full Prescribing Information" with its own section header "Usual Dosage" instead of under the header "Direction for Use".

5. Ensure that the placeholder "[active ingredient]" on all container labels and carton labeling will be updated to the correct nomenclature for the active ingredient.

Carton labeling

1. Revise the "Directions for Use" statements to include instructions on "If powder remains in the glass after drinking, they should add more water, stir, and then drink immediately. Repeated as needed to ensure the entire dose is administered."

2. For the (b) (4) size, relocate the "Directions for Use" statements from the side panel to the back panel and increase the font size of the text.

3. Remove or provide a rationale for the (b) (4) statement (b) (4) dispense as 1 box".

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Veltassa that Relypsa Inc. submitted on October 21, 2014.

Table 2. Relevant Product Information for Veltassa	
Initial Approval Date	N/A
Active Ingredient	patiromer
Indication	Veltassa is a potassium binder indicated for the treatment of hyperkalemia.
Route of Administration	Oral
Dosage Form	Oral suspension
Strength	(b) (4) 8.4 g, (b) (4) 16.8 g, (b) (4) and 25.2 g
Dose and Frequency	One packet given (b) (4) Maximum daily dose is (b) (4) patiromer (b) (4)
How Supplied	Powder for oral suspension packaged in single-use packets, which is supplied in cartons of (b) (4) single-use packets.
Storage	Veltassa should be stored in the refrigerator at 2°C to 8°C (36°F to 46°F). (b) (4) If stored at room temperature (b) (4) Veltassa must be used within 3 months of being taken out of the refrigerator. For either storage condition, do not use Veltassa after the expiration date printed on the packet.
Container Closure	(b) (4)

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with postmarket medication error data, we reviewed the following Veltassa labels and labeling submitted by Relypsa, Inc.

- Container label submitted on October 21, 2014
- Carton labeling submitted on October 21, 2014
- Prescribing Information submitted on December 9, 2014

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[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

JANINE A STEWART
02/12/2015

CHI-MING TU
02/13/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

<table>
<tr><th colspan="3">Application Information</th></tr>
<tr><td>NDA # 205739
BLA#</td><td>NDA Supplement #: S-
BLA Supplement #: S-</td><td>Efficacy Supplement Category:
☐ New Indication (SE1)
☐ New Dosing Regimen (SE2)
☐ New Route Of Administration (SE3)
☐ Comparative Efficacy Claim (SE4)
☐ New Patient Population (SE5)
☐ Rx To OTC Switch (SE6)
☐ Accelerated Approval Confirmatory Study (SE7)
☐ Animal Rule Confirmatory Study (SE7)
☐ Labeling Change With Clinical Data (SE8)
☐ Manufacturing Change With Clinical Data (SE9)
☐ Pediatric</td></tr>
<tr><td colspan="3">Proprietary Name: Veltassa
Established/Proper Name: Patiromer (RLY5016)
Dosage Form: Powder for Oral Suspension
Strengths: (b) (4) 8.4, (b) (4) 16.8, (b) (4) and 25 grams</td></tr>
<tr><td colspan="3">Applicant: Relypsa
Agent for Applicant (if applicable): NA</td></tr>
<tr><td colspan="3">Date of Application: October 21, 2014
Date of Receipt: October 21, 2014
Date clock started after UN: N/A</td></tr>
<tr><td colspan="2">PDUFA Goal Date: October 21, 2015</td><td>Action Goal Date (if different): N/A</td></tr>
<tr><td colspan="2">Filing Date: December 20, 2014</td><td>Date of Filing Meeting: December 4, 2014</td></tr>
<tr><td colspan="3">Chemical Classification (original NDAs only) :
☒ Type 1- New Molecular Entity (NME); NME and New Combination
☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination
☐ Type 3- New Dosage Form; New Dosage Form and New Combination
☐ Type 4- New Combination
☐ Type 5- New Formulation or New Manufacturer
☐ Type 7- Drug Already Marketed without Approved NDA
☐ Type 8- Partial Rx to OTC Switch</td></tr>
<tr><td colspan="3">Proposed indication(s)/Proposed change(s): treatment of hyperkalemia</td></tr>
<tr><td colspan="2">Type of Original NDA:
AND (if applicable)
Type of NDA Supplement:

If 505(b)(2): Draft the “505(b)(2) Assessment” review found at:
http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.</td><td>☒ 505(b)(1)
☐ 505(b)(2)
☐ 505(b)(1)
☐ 505(b)(2)</td></tr>
</table>

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 75615	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking***	☒	☐		

system.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	Review Priority= S
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) (NDAs/NDA Efficacy Supplements only)	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form, cover letter, and annotated labeling).* **If yes**, answer the bulleted	☐	☒		

questions below:				
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☒		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [**see 21 CFR 314.54(b)(1)].**	☐	☒		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [**see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☒		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☒		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☒	☐	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested (b) (4) ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☒	☐	☐	

NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☐	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM*** ***Note**: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible	☒	☐		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☐	

Forms and Certifications

Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*

Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☒	☐		

Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e.,"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting[2]*** ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and*	☒	☐		

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829 htm

pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☒	☐	☐	Submitted to IND 75,615 on Oct 20, 2014
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837 htm

Is the PI submitted in PLR format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☐	☐	☒	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☐	☐	☒	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

End-of Phase 2 meeting(s)? **Date(s):** 11/22/2011 ***If yes, distribute minutes before filing meeting***	☒	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 03/04/2014 ***If yes, distribute minutes before filing meeting***	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** 12/26/2012 ***If yes, distribute letter and/or relevant minutes before filing meeting***	☒	☐		

ATTACHMENT

MEMO OF FILING MEETING

DATE: December 4, 2014

BACKGROUND: Veltassa (Patiromer) is a new chemical entity that belongs to the pharmacologic class of Potassium Binders. It is a non-absorbed, cation-exchange polymer that binds potassium in the lumen of the colon and increasese fecal potassium excretion. A pre-NDA meeting was held on March 4, 2014.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Edward Fromm	Y
	CPMS/TL:	Edward Fromm	
Cross-Discipline Team Leader (CDTL)	Aliza Thompson		Y
Division Director/Deputy	Norman Stockbridge		Y
Office Director/Deputy	Ellis Unger		Y
Clinical	Reviewer:	Shen Xiao	Y
	TL:	Aliza Thompson	Y
Social Scientist Review (*for OTC products*)	Reviewer:		NA
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		NA
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Ju Ping Lai	Y
	TL:	Raj Madabushi	Y
Biostatistics	Reviewer:	Fanhui Kong	Y
	TL:	James Hung	N

Nonclinical (Pharmacology/Toxicology)	Reviewer:	William T. Link	Y
	TL:	Al DeFelice	Y
Statistics (carcinogenicity)	Reviewer:		NA
	TL:		
Immunogenicity (assay/assay validation) *(for protein/peptide products only)*	Reviewer:		NA
	TL:		
Product Quality (CMC)	Reviewer:	Mohan Sapru (Drug Prod) R.Frankewich	Y
	TL:	Kasturi Srinivasachar	Y
Biopharmaceutics	Reviewer	Chikhale, Elsbeth	Y
	TL:	Angelica Dorantes	N
Quality Microbiology	Reviewer:	Erica Pfeiler	N
	TL:	Brian Riley	N
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Vipul Dholakia	Y
	TL:		
OSE/DMEPA (proprietary name, carton/container labels))	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		NA
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		NA
	TL:		
Other reviewers/disciplines	Reviewer:		
	TL:		
Other attendees			

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., BA/BE studies):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO

• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason: NDA did not raise Saftey/Efficacy issues
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (protein/peptide products only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
New Molecular Entity (NDAs only) • Is the product an NME?	 ☒ YES ☐ NO
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> • Was the Microbiology Team consulted for validation of sterilization? **Comments**: Not a parenteral product	☐ Not Applicable ☒ YES ☐ NO

Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**: 	 ☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☐ N/A ☐ YES ☒ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO

• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Robert Temple, M.D.

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V): TBD

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. Review Classification: ☒ Standard Review ☐ Priority Review

ACTIONS ITEMS

☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	351(k) BLA/supplement: If filed, send filing notification letter on day 60
☐	If priority review:

	• notify sponsor in writing by day 60 (see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☒	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: September 2014

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

/s/

EDWARD J FROMM
12/30/2014