SUPPLEMENT TO
FIRST REPORT Managed Care®
PRODUCT BULLETIN

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Hyperkalemia, or high potassium, is a potentially life-threatening condition that is defined as a serum potassium above a certain level, generally >5.0 mEq/L, resulting in serious clinical complications.[1,2] Greater degrees of hyperkalemia may lead to cardiac arrhythmias and cardiac arrest, with increased mortality.[3] Individuals at highest risk for hyperkalemia include those with chronic kidney disease (CKD) stage 3-5, heart failure, underlying comorbidities, and use of renin–angiotensin–aldosterone system (RAAS) inhibitors.[2-5] Approximately 3 million people with CKD and/or heart failure in the United States have hyperkalemia.[6-10]

Hyperkalemia may result from an extracellular shift in potassium, increased intake, or decreased excretion, usually in the setting of poor kidney function.[11] Some medications prescribed to individuals with CKD and heart failure may compound the hyperkalemia risk such as nonsteroidal anti-inflammatory drugs and beta-blockers.[1] RAAS inhibitors, often prescribed to people with CKD and heart failure, are a well-documented class of drugs that can cause hyperkalemia. Commonly prescribed RAAS inhibitors include angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers.[1,12,13] Hyperkalemia is often asymptomatic, but can result in life-threatening effects on cardiac conduction, arrhythmias such as ventricular fibrillation and sudden death.[14,15]

MANAGING HYPERKALEMIA

Treatment of hyperkalemia centers on lowering the serum potassium levels, preventing recurrences, and monitoring patient safety. Dietary restriction of potassium is also an important component; however, many high-potassium foods may remain unrecognized by patients and health care providers.[1,12] Management should be guided by the clinical scenario and serial measurements of serum potassium concentration. Appropriate treatment of hyperkalemia is determined by the rate of change in serum potassium levels, severity level, and development of clinical findings.[1,3,16] For acute management

of hyperkalemia, certain cases may require emergent treatment with fast-acting medications to shift potassium levels back into cells and protect the heart.[2]

In terms of ongoing management, treatment options have been limited and include discontinuation or reduced doses of RAAS inhibitors, use of loop diuretics, restriction of dietary potassium, or use of sodium polystyrene sulfonate (SPS). However, these approaches have limitations and new approaches are needed. Reducing or discontinuing RAAS inhibitors means potentially withholding life saving or kidney preserving therapy. SPS was approved over 50 years ago and has limited safety and efficacy data with regard to ongoing use.[3,12] Additionally, in 2009, the FDA issued a warning to the SPS label regarding reports of potentially fatal intestinal necrosis, as well as other serious gastrointestinal adverse events.[17] The average daily adult dose of SPS is 15 g to 60 g. This is provided by administering 15 g of SPS 1 to 4 times daily. SPS contains approximately 100 mg of sodium per gram of drug. A single dose of SPS contains approximately 1.4 g of sodium. Because sodium is the counterion for the resin, the SPS label suggests caution in patients who cannot tolerate even a small increase in sodium loads and for whom an increase in sodium load may be detrimental (ie, severe congestive heart failure, severe hypertension, marked edema, or renal dysfunction).[3,12,18]

INDICATION AND LIMITATION OF USE

VELTASSA® is indicated for the treatment of hyperkalemia.[19]
VELTASSA should not be used as an emergency treatment for life-threatening hyperkalemia because of its delayed onset of action.

Important Safety Information

WARNING: BINDING TO OTHER ORAL MEDICATIONS

Veltassa binds to many orally administered medications, which could decrease their absorption and reduce their effectiveness. Administer other oral medications at least 6 hours before or 6 hours after Veltassa. Choose Veltassa or the other oral medication if adequate dosing separation is not possible.

Please see additional Important Safety Information starting below and full Prescribing Information on pages 7-16.

MECHANISM OF ACTION

VELTASSA is a nonabsorbed, cation exchange polymer that uses calcium as the counter-exchange ion, instead of sodium. It increases fecal potassium excretion through binding of potassium in the lumen of the gastrointestinal tract. Binding of potassium reduces the concentration of free potassium in the gastrointestinal lumen, resulting in a reduction of serum potassium levels.[19]

PHARMACOKINETICS

It has been shown through radiolabeled absorption, distribution, metabolism, and excretion (ADME) studies utilizing rats and dogs that VELTASSA is not systemically absorbed and is excreted through the feces. Furthermore, a quantitative whole-body autoradiography analysis in rats demonstrated that detected radioactivity was limited to the gastrointestinal tract with no detectable level of radioactivity in any other tissues or organs. Decrease in absorption of other medications may occur as a result of VELTASSA binding to orally administered medications in the gastrointestinal tract. In in vitro binding studies, VELTASSA was shown to bind about half of the oral medications that were tested.[19]

DOSING AND ADMINISTRATION

Binding of VELTASSA to other oral medications could cause decreased gastrointestinal absorption and loss of efficacy when taken close to the time VELTASSA is administered. Other oral medications should be administered at least 6 hours before or 6 hours after VELTASSA. Choose VELTASSA or the other oral medication if adequate dosing separation is not possible. VELTASSA should be administered with food and should not be heated (eg, microwave) or added to heated foods or liquids. Furthermore, VELTASSA should not be taken in its dry form. Monitor serum potassium and adjust the dose of VELTASSA based on the serum potassium level and the desired target range.[19]

VELTASSA CLINICAL TRIAL DATA

In clinical trials, VELTASSA significantly reduced blood potassium levels to the target range for up to a year in patients with hyperkalemia, allowing for ongoing daily treatment of hyperkalemia.[19-22]

OPAL-HK STUDY

The efficacy of VELTASSA was demonstrated in OPAL-HK—a 2 part, single-blind, randomized, withdrawal, phase 3 study that evaluated VELTASSA in 237 patients with

IMPORTANT SAFETY INFORMATION

WARNING: BINDING TO OTHER ORAL MEDICATIONS

VELTASSA binds to many orally administered medications, which could decrease their absorption and reduce their effectiveness. Administer other oral medications at least 6 hours before or 6 hours after VELTASSA. Choose VELTASSA or the other oral medication if adequate dosing separation is not possible.

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hyperkalemia and CKD on stable doses of at least one RAAS inhibitor (ie, ACE inhibitor, angiotensin II receptor blocker, or aldosterone antagonist). The first part of the study was a 4-week, single-arm, single-blind initial treatment period; the second part was an 8-week, placebo-controlled, single-blind, randomized, withdrawal period. The mean age of patients was 64 years, 58% of patients were male, and 98% were white. Approximately 97% of patients had hypertension, 57% had type 2 diabetes, and 42% had heart failure.[19,20]

In the initial treatment period, patients were randomized to 1 of 2 VELTASSA starting doses according to hyperkalemia severity. Patients with a baseline serum potassium of 5.1 mEq/L to <5.5 mEq/L received 8.4 g of VELTASSA per day (as a divided dose; n=90), and those with a baseline serum potassium of 5.5 mEq/L to <6.5 mEq/L received 16.8 g of VELTASSA per day (as a divided dose; n=147). The dose of VELTASSA was titrated, as needed, based on the serum potassium level that was assessed starting on day 3 and then at weekly visits (weeks 1, 2, and 3) to the end of the 4-week treatment period, with the aim of maintaining serum potassium in the target range (3.8 mEq/L to <5.1 mEq/L). The mean daily doses of VELTASSA were 13 g and 21 g in patients with serum potassium of 5.1 mEq/L to <5.5 mEq/L and 5.5 mEq/L to <6.5 mEq/L, respectively. The primary efficacy endpoint was the mean change in serum potassium level from baseline to week 4. The secondary efficacy endpoint was the proportion of patients who had a serum potassium in the target range of 3.8 to <5.1.[19,20]

At the end of week 4, 107 eligible patients (those with a Part A baseline potassium level of 5.5 mEq/L to <6.5 mEq/L in whom the level decreased to 3.8 mEq/L to <5.1 mEq/L) still receiving RAAS inhibitor medication entered an 8-week randomized, withdrawal period. Patients were randomized 1:1 to continue VELTASSA (n=55) at the same daily dose they were receiving at week 4 of the initial treatment period or to receive placebo (n=52) to evaluate the effect of withdrawing VELTASSA on serum potassium. In patients randomized to VELTASSA, the mean daily dose at the start of part B and during part B was 21 g. The primary efficacy endpoint was the between-group difference in the median change in serum potassium level over the first 4 weeks of that period or to the earliest visit at which the patient's serum potassium level was first outside the range of <3.8 mEq/L to <5.5 mEq/L or higher. The secondary endpoints were the proportion of patients with a recurrence of hyperkalemia according to 2 definitions: a serum potassium level of 5.1 mEq/L or higher and a serum potassium level of 5.5 mEq/L or higher.[19,20]

In the initial treatment period, VELTASSA significantly decreased potassium levels (mean decrease 1.01 ± 0.03 mEq/L from baseline; $P<.001$). The change in patients with mild hyperkalemia was a decrease of 0.65 ± 0.05 mEq/L (95% confidence interval [CI], −0.74 to −0.55), and the change in those with moderate-to-severe hyperkalemia was a decrease of 1.23 ± 0.04 mEq/L (95% CI, −1.31 to −1.16). At week 4, 76% of patients had potassium levels in the target range (3.8 mEq/L to <5.1 mEq/L). During the randomized, withdrawal period, patients taking VELTASSA had no change in median potassium from baseline compared with an increase in the placebo group (0.00 vs 0.72 mEq/L, respectively; $P<.001$). Hyperkalemia recurred in more patients who were switched to placebo versus the VELTASSA treatment arm through week 8 (60% vs 15%, respectively).[19,20]

AMETHYST-DN STUDY

The effect of treatment with VELTASSA for up to 52 weeks was evaluated in AMETHYST-DN. The multicenter, open-label, dose-ranging, randomized, phase 2 study included 304 hyperkalemic patients with CKD and type 2 diabetes on RAAS therapy prior to and during study treatment. The study consisted of a screening visit, a run-in period of up to 4 weeks' duration, an 8-week treatment period followed by a long-term maintenance phase of up to 44 weeks' duration (up to 52 weeks of total treatment), and a posttreatment follow-up period of up to 4 weeks' duration. The mean age of patients was 66.3 years, 63.2% were male, and 100% were white. All patients had hypertension and

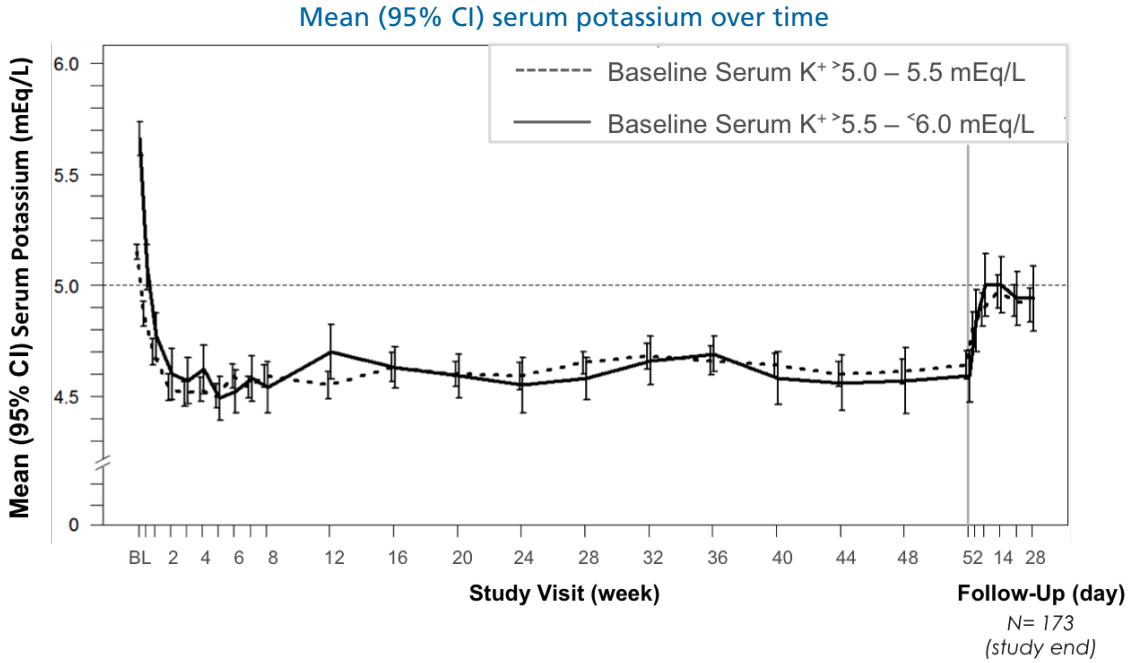
IMPORTANT SAFETY INFORMATION (continued)

Contraindications VELTASSA is contraindicated in patients with a history of a hypersensitivity reaction to VELTASSA or any of its components.

Worsening of Gastrointestinal Motility Avoid use of VELTASSA in patients with severe constipation, bowel obstruction or impaction, including abnormal post-operative bowel motility disorders, because VELTASSA may be ineffective and may worsen gastrointestinal conditions. Patients with a history of bowel obstruction or major gastrointestinal surgery, severe gastrointestinal disorders, or swallowing disorders were not included in clinical studies.

See additional Important Safety Information, including Boxed WARNING, throughout this article, and accompanying full Prescribing Information on pages 7-16.

Figure. AMETHYST-DN, One-Year Study[19]



type 2 diabetes, 65% had stage 3 CKD and 22% had stage 4 CKD, and 35% had heart failure.[19,21]

Patients were stratified by baseline serum potassium level into mild or moderate hyperkalemia groups and randomized 1:1:1 to 1 of 3 VELTASSA starting doses (mild hyperkalemia: 8.4 g [n=74], 16.8 g [n=74], or 25.2 g [n=74] total daily doses [given as a divided dose]; moderate hyperkalemia: 16.8 g [n=26], 25.2 g [n=28], or 33.6 g [n=30] total daily doses [given as a divided dose]). VELTASSA was titrated to achieve and maintain serum potassium level 5.0 mEq/L or lower within limits. In patients with a baseline serum potassium of >5.0 mEq/L to 5.5 mEq/L who received an initial dose of 8.4 g VELTASSA per day (as a divided dose), the mean daily dose was 14 g; in those with a baseline serum potassium of >5.5 mEq/L to 6.0 mEq/L who received an initial dose of 16.8 g VELTASSA per day (as a divided dose), the mean daily dose was 20 g during the entire study. The primary efficacy endpoint was mean change in serum potassium level from baseline to week 4 or prior to initiation of dose titration. The primary safety endpoint was the frequency and severity of adverse events through the end of the maintenance period at week 52. Secondary efficacy endpoints included the mean change in serum potassium level from baseline to other postbaseline visits.[19,21]

VELTASSA starting doses of 8.4 g daily (given as a divided dose) to 33.6 g (given as a divided dose) resulted in statistically significant decreases in serum potassium level after 4 weeks of treatment, lasting through 52 weeks (**Figure**). The least squares mean reduction from baseline in serum potassium level at week 4 or time of first dose titration in patients with mild hyperkalemia was 0.35 mEq/L for the 8.4 g/d group, 0.51 mEq/L for the 16.8 g/d group, and 0.55 mEq/L for the 25.2 g/d group. In those with moderate hyperkalemia, the least squares mean reduction from baseline in serum potassium level at week 4 or at the time of first dose titration was 0.87

IMPORTANT SAFETY INFORMATION (continued)

Hypomagnesemia VELTASSA binds to magnesium in the colon, which can lead to hypomagnesemia. In clinical studies, hypomagnesemia was reported as an adverse reaction in 5.3% of patients treated with VELTASSA. Approximately 9% of patients in clinical trials developed hypomagnesemia with a serum magnesium value <1.4 mg/dL. Monitor serum magnesium. Consider magnesium supplementation in patients who develop low serum magnesium levels.

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mEq/L for 16.8 g/d group, 0.97 mEq/L for the 25.2 g/d group, and 0.92 mEq/L for the 33.6 g/d group. Over 52 weeks, hypomagnesemia (7.2%) was the most common treatment-related adverse event, constipation (4.6%) was the most common gastrointestinal adverse event, and hypokalemia (<3.5 mEq/L) occurred in 5.6% of patients.[19,21]

ONSET OF ACTION STUDY

An open-label, single-arm, phase 1 study evaluated VELTASSA's onset of action in 25 hyperkalemic patients with CKD who were receiving at least one RAAS inhibitor. After a 3-day potassium- and sodium-restricted diet run-in period in an inpatient unit, patients with a serum potassium of 5.5 mEq/L to <6.5 mEq/L entered the treatment period and began VELTASSA 16.8 g daily as a divided dose with meals for 2 days, for a total of 4 doses. All patients received the same dosage of VELTASSA regardless of their serum potassium. Serum potassium was assessed at baseline (0 hour), 4-hour postdose, then every 2 to 4 hours to 48 hours, at 58 hours, and during outpatient follow-up. The patients were predominately male with a mean age of 58.7 years. The mean duration of CKD was 4.49 years, with the majority of patients having moderate to severe CKD.[22]

A statistically significant reduction in potassium levels was first observed at 7 hours after the first dose. From a mean baseline serum potassium of 5.93 mEq/L, a significant reduction of 0.21 mEq/L (95% CI −0.35,−0.07; P=.004) occurred 7 hours after the first VELTASSA dose. Potassium levels continued to decline during the 48-hour treatment period of the study. At 48 hours, after 4 doses of VELTASSA, mean serum potassium had fallen by 0.75 mEq/L, and more than 90% of patients had serum potassium values ≤5.5 mEq/L. For the secondary endpoint, in a prespecified secondary analysis, mean changes in serum potassium over time in patients with moderate and severe hyperkalemia were consistent with those seen in the overall population. For patients with moderate and severe hyperkalemia, the mean change from baseline at 7 hours was -0.17 mEq/L and -0.29 mEq/L, respectively.[2]

VELTASSA SAFETY AND TOLERABILITY INFORMATION

In the safety and efficacy clinical trials, 666 adult patients received at least 1 dose of VELTASSA, including 219 exposed for at least 6 months and 149 exposed for at least 1 year. In clinical trials, most adverse reactions were mild to moderate. The most common adverse reactions reported in ≥2% of patients in clinical trials are shown in the **Table**.[19]

During the clinical studies, the most commonly reported adverse reactions leading to discontinuation of VELTASSA were gastrointestinal adverse reactions (2.7%) including vomiting (0.8%), diarrhea (0.6%), constipation (0.5%), and flatulence (0.5%). Mild to moderate hypersensitivity reactions were reported in 0.3% of patients treated with VELTASSA in clinical trials. Reactions have included edema of the lips. Approximately 4.7% of patients in clinical trials developed hypokalemia with a serum potassium value <3.5 mEq/L. Approximately 9% of patients in clinical trials developed hypomagnesemia with a serum magnesium value <1.4 mg/dL.[19]

Table. Adverse Reactions Reported in ≥2% of Patients[19]

Adverse Reactions	Patients Treated With VELTASSA (N=666)
Constipation	7.2%
Hypomagnesemia	5.3%
Diarrhea	4.8%
Nausea	2.3%
Abdominal discomfort	2.0%
Flatulence	2.0%

DOSAGE AND ADMINISTRATION (continued)

The recommended starting dose of VELTASSA is 8.4 g once daily. Clinicians should monitor serum potassium and adjust the dose of VELTASSA based on the serum potassium level and the desired target range. The dose may be increased or decreased, as necessary, to reach the desired serum potassium concentration, up to a maximum dose of 25.2 g once daily. The dose can be titrated up based on serum potassium level at 1-week or longer intervals,

IMPORTANT SAFETY INFORMATION (continued)

Adverse Reactions The most common adverse reactions (incidence ≥2%) are constipation, hypomagnesemia, diarrhea, nausea, abdominal discomfort, and flatulence. Mild to moderate hypersensitivity reactions were reported in 0.3% of patients treated with VELTASSA and included edema of the lips.

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in increments of 8.4 g. Individuals should administer VELTASSA at least 6 hours before or 6 hours after other oral medications. It should be taken with food. VELTASSA should not be heated or added to heated foods or liquids. It should not be taken in its dry form.[19]

Individuals should prepare each dose of VELTASSA immediately prior to administration following these 6 steps regardless of dose:[19]

Step 1. Add about 1 oz (30 mL) of water to an empty glass or cup.

Step 2. Empty the entire contents of the packet(s) into the glass or cup.

Step 3. Stir the mixture thoroughly.

Step 4. Add an additional 2 oz (60 mL) of water to the glass or cup containing the mixture.

Step 5. Stir the mixture thoroughly; the powder will not dissolve and the mixture will look cloudy.

Step 6. Drink the mixture immediately. If some powder remains in the glass after drinking, add more water, stir, and drink immediately. Repeat as needed to ensure the entire dose is administered.

SUMMARY

Hyperkalemia is a complex medical condition with potentially serious cardiovascular consequences for patients with CKD, heart failure, or diabetes.[1,12] Managing hyperkalemia is a challenge for clinicians because some medications prescribed to individuals with CKD with or without heart failure to help delay disease progression can cause hyperkalemia as a side effect, leaving clinicians with limited treatment options.

The FDA approval of VELTASSA marks the first new medicine for hyperkalemia in more than 50 years, offering clinicians an alternative therapy for the ongoing, daily treatment of hyperkalemia. VELTASSA uses calcium as the counter-exchange ion, instead of sodium. Data from clinical studies showed that VELTASSA significantly reduced blood potassium and kept levels in target range for up to a year in patients with hyperkalemia. The most common adverse reactions are constipation, hypomagnesemia, diarrhea, nausea, abdominal discomfort, and flatulence.

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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use VELTASSA™ safely and effectively. See full prescribing information for VELTASSA.

VELTASSA (patiromer) for oral suspension
Initial U.S. Approval: 2015

WARNING: BINDING TO OTHER ORAL MEDICATIONS

Veltassa binds to many orally administered medications, which could decrease their absorption and reduce their effectiveness. Administer other oral medications at least 6 hours before or 6 hours after Veltassa. Choose Veltassa or the other oral medication if adequate dosing separation is not possible. (2.1, 5.1, 7)

----------INDICATIONS AND USAGE----------

Veltassa is a potassium binder indicated for the treatment of hyperkalemia. (1)

Limitation of Use
Veltassa should not be used as an emergency treatment for life-threatening hyperkalemia because of its delayed onset of action. (1)

---------- DOSAGE AND ADMINISTRATION ----------

- The recommended starting dose of Veltassa is 8.4 grams administered orally once daily with food. (2.2)
- Adjust dose by 8.4 grams daily as needed at one week intervals to obtain desired serum potassium target range. (2.2)

---------- DOSAGE FORMS AND STRENGTHS ----------

- Powder: 8.4, 16.8 and 25.2 grams patiromer packets. (3)

----------CONTRAINDICATIONS----------

- Known hypersensitivity to Veltassa or any of its components. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Worsening of Gastrointestinal Motility (5.2)
- Hypomagnesemia (5.3)

---------- ADVERSE REACTIONS ----------

- Most common adverse reactions (incidence ≥ 2%) are constipation, hypomagnesemia, diarrhea, nausea, abdominal discomfort and flatulence. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Relypsa at 1-844-VELTASSA (1-844-835-8277) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

- Take other orally administered drugs at least 6 hours before or 6 hours after Veltassa. (2.1, 5.1, 7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: [10/2015]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: BINDING TO OTHER ORAL MEDICATIONS

Veltassa binds to many orally administered medications, which could decrease their absorption and reduce their effectiveness. Administer other oral medications at least 6 hours before or 6 hours after Veltassa. Choose Veltassa or the other oral medication if adequate dosing separation is not possible *[see Dosage and Administration (2.1), Warnings and Precautions (5.1) and Drug Interactions (7)].*

1 INDICATIONS AND USAGE

Veltassa is indicated for the treatment of hyperkalemia.

Limitation of Use: Veltassa should not be used as an emergency treatment for life-threatening hyperkalemia because of its delayed onset of action *[see Pharmacodynamics (12.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 General Information

Administer Veltassa at least 6 hours before or 6 hours after other oral medications *[see Warnings and Precautions (5.1) and Drug Interactions (7)].*

Administer Veltassa with food. Do not heat Veltassa (e.g., microwave) or add to heated foods or liquids. Do not take Veltassa in its dry form.

2.2 Recommended Dosing and Titration

The recommended starting dose of Veltassa is 8.4 grams patiromer once daily. Monitor serum potassium and adjust the dose of Veltassa based on the serum potassium level and the desired target range. The dose may be increased or decreased, as necessary, to reach the desired serum potassium concentration, up to a maximum dose of 25.2 grams once daily. The dose can be up-titrated based on serum potassium level at 1-week or longer intervals, in increments of 8.4 grams.

2.3 Preparation of Veltassa

Prepare each dose immediately prior to administration following the steps below:

Step 1: Add about 1 ounce (30 milliliters) of water to an empty glass or cup.

Step 2: Empty the entire contents of the packet(s) into the glass or cup.

Step 3: Stir the mixture thoroughly.

Step 4: Add an additional 2 ounces (60 milliliters) of water to the glass or cup containing the mixture.

Step 5: Stir the mixture thoroughly; the powder will not dissolve and the mixture will look cloudy.

Step 6: Drink the mixture immediately. If some powder remains in the glass after drinking, add more water, stir and drink immediately. Repeat as needed to ensure the entire dose is administered.

3 DOSAGE FORMS AND STRENGTHS

Veltassa is an off-white to light-brown powder for oral suspension packaged in single-use packets containing 8.4 grams, 16.8 grams or 25.2 grams patiromer.

4 CONTRAINDICATIONS

Veltassa is contraindicated in patients with a history of a hypersensitivity reaction to Veltassa or any of its components *[see Adverse Reactions (6.1)].*

5 WARNINGS AND PRECAUTIONS

5.1 Binding to Other Orally Administered Medications

Veltassa binds many orally administered medications, which could decrease their gastrointestinal absorption and lead to reduced efficacy. Administer other oral medications at least 6 hours before or 6 hours after Veltassa. Choose Veltassa or the other oral medication if adequate dosing separation is not possible *[see Dosage and Administration (2.1) and Drug Interactions (7)]*.

5.2 Worsening of Gastrointestinal Motility

Avoid use of Veltassa in patients with severe constipation, bowel obstruction or impaction, including abnormal post-operative bowel motility disorders, because Veltassa may be ineffective and may worsen gastrointestinal conditions.

Patients with a history of bowel obstruction or major gastrointestinal surgery, severe gastrointestinal disorders, or swallowing disorders were not included in the clinical studies.

5.3 Hypomagnesemia

Veltassa binds to magnesium in the colon, which can lead to hypomagnesemia. In clinical studies, hypomagnesemia was reported as an adverse reaction in 5.3% of patients treated with Veltassa *[see Adverse Reactions (6.1)].* Monitor serum magnesium. Consider magnesium supplementation in patients who develop low serum magnesium levels on Veltassa.

6 ADVERSE REACTIONS

The following adverse reaction is discussed in greater detail elsewhere in the label:

- Hypomagnesemia *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of Veltassa cannot be directly compared to rates in the clinical trials of other drugs and may not reflect the rates observed in practice.

In the safety and efficacy clinical trials, 666 adult patients received at least one dose of Veltassa, including 219 exposed for at least 6 months and 149 exposed for at least one year.

Table 1 provides a summary of the most common adverse reactions (occurring in ≥ 2% of patients) in patients treated with Veltassa in these clinical trials. Most adverse reactions were mild to moderate. Constipation generally resolved during the course of treatment.

Table 1: Adverse Reactions Reported in ≥ 2% of Patients

Adverse Reactions	Patients treated with Veltassa (N=666)
Constipation	7.2%
Hypomagnesemia	5.3%
Diarrhea	4.8%
Nausea	2.3%
Abdominal discomfort	2.0%
Flatulence	2.0%

During the clinical studies, the most commonly reported adverse reactions leading to discontinuation of Veltassa were gastrointestinal adverse reactions (2.7%), including vomiting (0.8%), diarrhea (0.6%), constipation (0.5%) and flatulence (0.5%).

Mild to moderate hypersensitivity reactions were reported in 0.3% of patients treated with Veltassa in clinical trials. Reactions have included edema of the lips.

Laboratory Abnormalities

Approximately 4.7% of patients in clinical trials developed hypokalemia with a serum potassium value < 3.5 mEq/L.

Approximately 9% of patients in clinical trials developed hypomagnesemia with a serum magnesium value < 1.4 mg/dL.

7 DRUG INTERACTIONS

No formal drug interaction studies have been conducted in humans.

In *in vitro* binding studies, Veltassa was shown to bind about half of the oral medications that were tested. Binding of Veltassa to other oral medications could cause decreased gastrointestinal absorption and loss of efficacy when taken close to the time Veltassa is administered. Administer other oral medications at least 6 hours before or 6 hours after Veltassa. Monitor for clinical response and/or blood levels where possible.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Veltassa is not absorbed systemically following oral administration and maternal use is not expected to result in fetal risk.

8.2 Lactation

Risk Summary

Veltassa is not absorbed systemically by the mother, so breastfeeding is not expected to result in risk to the infant.

8.4 Pediatric Use

Safety and efficacy in pediatric patients have not been established.

8.5 Geriatric Use

Of the 666 patients treated with Veltassa in clinical studies, 59.8% were age 65 and over, and 19.8% were age 75 and over. No overall differences in effectiveness were observed between these patients and younger patients. Patients age 65 and older reported more gastrointestinal adverse reactions than younger patients.

8.6 Renal Impairment

Of the 666 patients treated with Veltassa in clinical studies, 93% had chronic kidney disease (CKD). No special dosing adjustments are needed for patients with renal impairment.

10 OVERDOSAGE

Doses of Veltassa in excess of 50.4 grams per day have not been tested. Excessive doses of Veltassa may result in hypokalemia. Restore serum potassium if hypokalemia occurs.

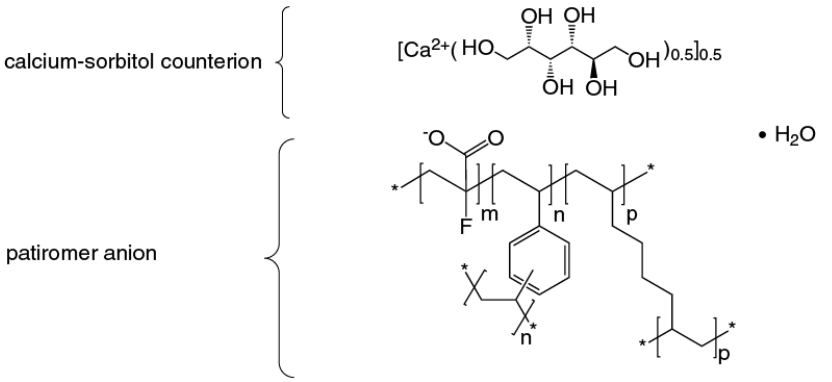
11 DESCRIPTION

Veltassa is a powder for suspension in water for oral administration. The active ingredient is patiromer sorbitex calcium which consists of the active moiety, patiromer, a non-absorbed potassium-binding polymer, and a calcium-sorbitol counterion. Each gram of patiromer is equivalent to a nominal amount of 2 grams of patiromer sorbitex calcium.

The chemical name for patiromer sorbitex calcium is cross-linked polymer of calcium 2-fluoroprop-2-enoate with diethenylbenzene and octa-1,7-diene, combination with D-glucitol.

Patiromer sorbitex calcium is an amorphous, free-flowing powder that is composed of individual spherical beads. Patiromer sorbitex calcium is insoluble in solvents such as water, 0.1 M HCl, n-heptane and methanol. The chemical structure of patiromer sorbitex calcium is presented in Figure 1.

Figure 1: Chemical Structure of Patiromer Sorbitex Calcium



m = number of 2-fluoro-2-propenoate groups m = 0.91

n, p = number of crosslinking groups n + p = 0.09

•H_2O = associated water

* = indicates an extended polymeric network

Each packet of Veltassa contains 8.4 grams, 16.8 grams or 25.2 grams of patiromer, the active moiety. The inactive ingredient is xanthan gum.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Veltassa is a non-absorbed, cation exchange polymer that contains a calcium-sorbitol counterion.

Veltassa increases fecal potassium excretion through binding of potassium in the lumen of the gastrointestinal tract. Binding of potassium reduces the concentration of free potassium in the gastrointestinal lumen, resulting in a reduction of serum potassium levels.

12.2 Pharmacodynamics

In a Phase 1 study in healthy adult subjects (6 to 8 subjects per group), Veltassa (0 grams to 50.4 grams per day) administered three times a day for 8 days caused a dose-dependent increase in fecal potassium excretion. A corresponding dose-dependent decrease in urinary potassium excretion with no change in serum potassium were also observed. Compared to placebo, Veltassa doses of 25.2 and 50.4 grams per day significantly decreased mean daily urinary potassium excretion.

In a Phase 1, open-label, multiple-dose crossover study in 12 healthy subjects, 25.2 grams of patiromer per day was administered orally as a once daily, twice daily or thrice daily regimen for 6 days in a randomly assigned order. A significant increase in mean daily fecal potassium excretion and concomitant decrease in mean daily urinary potassium excretion were observed during the treatment periods for all three dosing regimens. The mean increase in fecal potassium excretion ranged from 1283 to 1550 mg/day, and the mean decrease in urinary potassium excretion ranged from 1438 to 1534 mg/day across the three dosing regimens. No significant differences were observed among the dosing regimens with respect to mean daily fecal potassium and urinary potassium excretion. This was true for the overall comparison among the three dosing regimens, as well as for the pairwise comparisons.

In an open-label, uncontrolled study, 25 patients with hyperkalemia (mean baseline serum potassium of 5.9 mEq/L) and chronic kidney disease were given a controlled potassium diet for 3 days, followed by 16.8 grams patiromer daily (as divided doses) for 2 days while the controlled diet was continued. A statistically significant reduction in serum potassium (-0.2 mEq/L) was observed at 7 hours after the first dose. Serum potassium levels continued to decline during the 48-hour treatment period (-0.8 mEq/L at 48 hours after the first dose). Potassium levels remained stable for 24 hours after the last dose, then rose during the 4-day observation period following discontinuation of Veltassa.

12.3 Pharmacokinetics

In radiolabeled ADME studies in rats and dogs, patiromer was not systemically absorbed and was excreted in the feces. Quantitative whole-body autoradiography analysis in rats demonstrated that radioactivity was limited to the gastrointestinal tract, with no detectable level of radioactivity in any other tissues or organs.

Drug Interactions

Veltassa binds many other orally administered medications in the gastrointestinal tract, which could lead to a decrease in absorption of other medications.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Patiromer was not genotoxic in the reverse mutation test (Ames assay), chromosome aberration or rat micronucleus assays.

Carcinogenicity studies have not been performed.

Patiromer did not impair the fertility in male or female rats at doses up to 10-fold the maximum recommended human dose (MRHD).

14 CLINICAL STUDIES

14.1 Two-Part, Randomized Withdrawal Study

The efficacy of Veltassa was demonstrated in a two-part, single-blind randomized withdrawal study that evaluated Veltassa in hyperkalemic patients with CKD on stable doses of at least one renin-angiotensin-aldosterone system inhibitor (i.e., angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, or aldosterone antagonist).

In Part A, 243 patients were treated with Veltassa for 4 weeks. Patients with a baseline serum potassium of 5.1 mEq/L to < 5.5 mEq/L received a starting Veltassa dose of 8.4 grams patiromer per day (as a divided dose) and patients with a baseline serum potassium of 5.5 mEq/L to < 6.5 mEq/L received a starting Veltassa dose of 16.8 grams patiromer per day (as a divided dose). The dose of Veltassa was titrated, as needed, based on the serum potassium level, assessed starting on Day 3 and then at weekly visits (Weeks 1, 2 and 3) to the end of the 4-week treatment period, with the aim of maintaining serum potassium in the target range (3.8 mEq/L to < 5.1 mEq/L).

The mean age of patients was 64 years, 58% of patients were men, and 98% were Caucasian. Approximately 97% of patients had hypertension, 57% had type 2 diabetes, and 42% had heart failure.

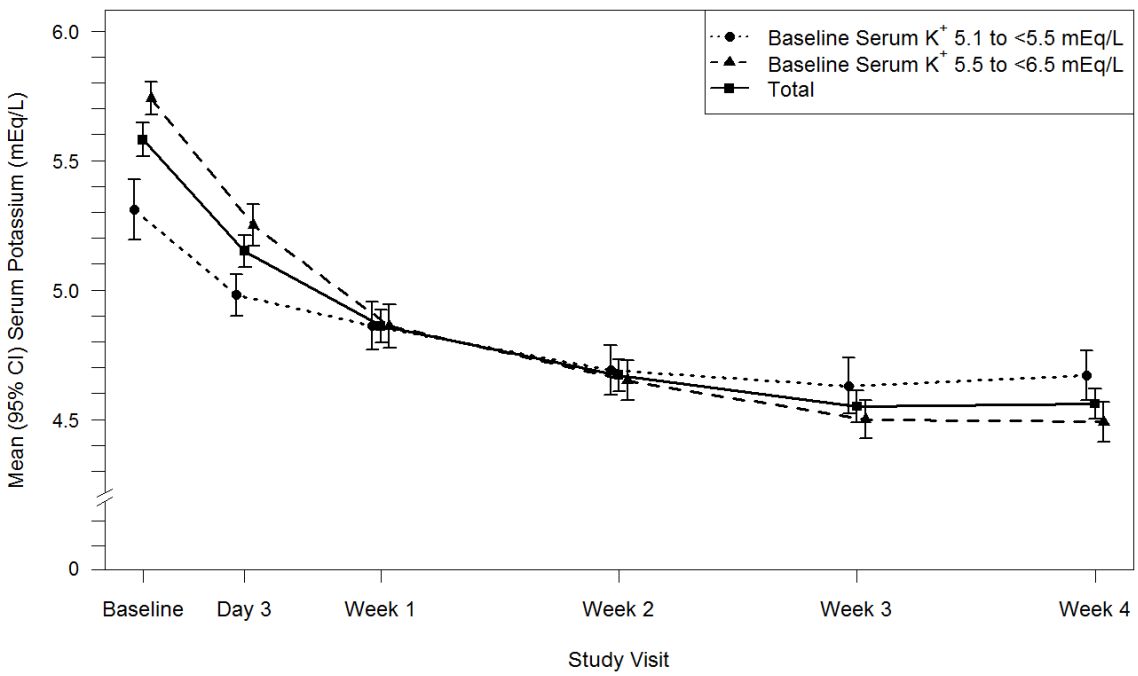
Results for the Part A primary endpoint, the change in serum potassium from Baseline to Week 4, are summarized in Table 2. Mean serum potassium over time for the intent-to-treat

population is displayed in Figure 2. For the Part A secondary endpoint, 76% (95% confidence interval [CI]: 70%, 81%) of patients had a serum potassium in the target range of 3.8 mEq/L to < 5.1 mEq/L at Week 4. The mean daily doses of Veltassa were 13 grams and 21 grams in patients with serum potassium of 5.1 to < 5.5 mEq/L and 5.5 to < 6.5 mEq/L, respectively.

Table 2: Veltassa Treatment Phase (Part A): Primary Endpoint

	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

Figure 2: Estimated Mean (95% CI) of Central Serum Potassium (mEq/L) Over Time



In Part B, 107 patients with a Part A baseline serum potassium of 5.5 mEq/L to < 6.5 mEq/L and whose serum potassium was in the target range (3.8 mEq/L to < 5.1 mEq/L) at Part A Week 4 and still receiving RAAS inhibitor medication were randomized to continue Veltassa or to receive placebo to evaluate the effect of withdrawing Veltassa on serum potassium. In patients randomized to Veltassa, the mean daily dose was 21 grams at the start of Part B and during Part B.

The Part B primary endpoint was the change in serum potassium from Part B baseline to the earliest visit at which the patient's serum potassium was first outside of the range of

3.8 to < 5.5 mEq/L, or to Part B Week 4 if the patient's serum potassium remained in the range. In Part B, serum potassium rose by 0.72 mEq/L in patients who were switched to placebo, versus no change in patients who remained on Veltassa. Results are summarized in Table 3.

Table 3: Randomized, Placebo-Controlled Withdrawal Phase (Part B): Primary Endpoint

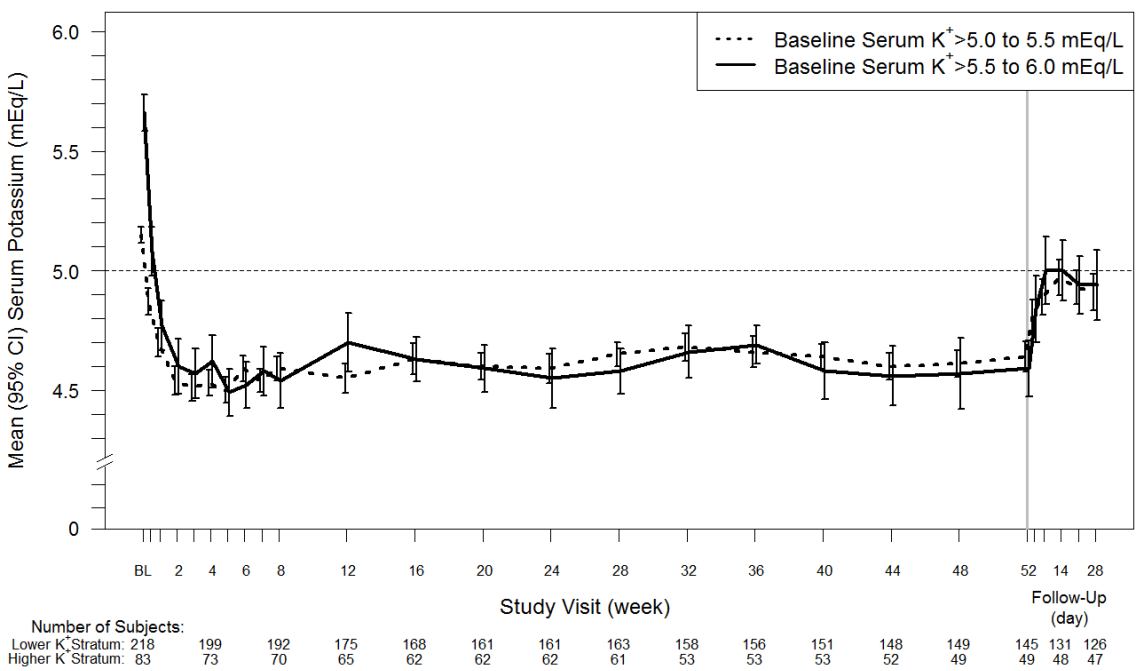
	Placebo (n=52)	Veltassa (n=55)	Difference	
			Estimate (95% CI)	*p*-value
Estimated Median Change in Serum Potassium from Baseline (mEq/L)	0.72	0.00	0.72 (0.46, 0.99)	< 0.001

More placebo patients (91%; 95% CI: 83%, 99%) developed a serum potassium ≥ 5.1 mEq/L at any time during Part B than Veltassa patients (43%; 95% CI: 30%, 56%), $p < 0.001$. More placebo patients (60%; 95% CI: 47%, 74%) developed a serum potassium ≥ 5.5 mEq/L at any time during Part B than Veltassa patients (15%; 95% CI: 6%, 24%), $p < 0.001$.

14.2 One-Year Study

The effect of treatment with Veltassa for up to 52 weeks was evaluated in an open-label study of 304 hyperkalemic patients with CKD and type 2 diabetes mellitus on RAAS inhibitor therapy. Figure 3 shows that the treatment effect on serum potassium was maintained during continued therapy. In patients with a baseline serum potassium of > 5.0 to 5.5 mEq/L who received an initial dose of 8.4 grams patiromer per day (as a divided dose), the mean daily dose was 14 grams; in those with a baseline serum potassium of > 5.5 to 6.0 mEq/L who received an initial dose of 17 grams patiromer per day (as a divided dose), the mean daily dose was 20 grams during the entire study.

Figure 3: Mean (95% CI) Serum Potassium over Time



16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Veltassa is supplied as a powder for oral suspension formulated with xanthan gum. Veltassa is packaged in single-use packets containing 8.4 grams, 16.8 grams or 25.2 grams patiromer as follows:

Veltassa (grams)	Single Use Packet	Carton of 4 Packets	Carton of 30 Packets
8.4	NDC 53436-084-01	NDC 53436-084-04	NDC 53436-084-30
16.8	NDC 53436-168-01	-	NDC 53436-168-30
25.2	NDC 53436-252-01	-	NDC 53436-252-30

16.2 Stability and Storage

Veltassa should be stored in the refrigerator at 2°C to 8°C (36°F to 46°F).

If stored at room temperature (25°C ± 2°C [77°F ± 4°F]), 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.

Avoid exposure to excessive heat above 40°C (104°F).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Drug Interactions

Advise patients who are taking other oral medication to separate the dosing of Veltassa by at least 6 hours (before or after) *[see Drug Interactions (7)].*

Dosing Recommendations

Inform patients to take Veltassa as directed with food and adhere to their prescribed diets. Instruct patients to prepare each dose separately using the preparation instructions provided in the FDA-approved patient labeling (Medication Guide).

Inform patients that Veltassa should not be heated (e.g., microwaved) or added to heated foods or liquids and should not be taken in its dry form.

Manufactured for:

Relypsa, Inc.
Redwood City, CA 94063

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