HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use RAVICTI safely and effectively. See full prescribing information for RAVICTI.

RAVICTI® (glycerol phenylbutyrate) oral liquid
Initial U.S. Approval: 1996

RECENT MAJOR CHANGES

Indications and Usage (1)	12/2018
Dosage and Administration (2.4)	12/2018
Contraindications (removed) (4)	12/2018
Warnings and Precautions (5.1)	12/2018

INDICATIONS AND USAGE

RAVICTI is a nitrogen-binding agent indicated for chronic management of patients with urea cycle disorders (UCDs) who cannot be managed by dietary protein restriction and/or amino acid supplementation alone. RAVICTI must be used with dietary protein restriction and, in some cases, dietary supplements. (1)

Limitations of Use:

- RAVICTI is not indicated for treatment of acute hyperammonemia in patients with UCDs. (1)
- Safety and efficacy for treatment of N-acetylglutamate synthase (NAGS) deficiency has not been established. (1)

DOSAGE AND ADMINISTRATION

- RAVICTI should be prescribed by a physician experienced in management of UCDs. For administration and preparation, see full prescribing information. (2.1, 2.6)

Switching From Sodium Phenylbutyrate Tablets or Powder to RAVICTI:

- Patients should receive the dosage of RAVICTI that contains the same amount of phenylbutyric acid, see full prescribing information for conversion. (2.2)

Initial Dosage in Phenylbutyrate-Naïve Patients (2.3):

- Recommended dosage range is 4.5 to 11.2 mL/m^2/day (5 to 12.4 g/m^2/day).
- For patients with some residual enzyme activity not adequately controlled with dietary restriction, the recommended starting dose is 4.5 mL/m^2/day.
- Take into account patient's estimated urea synthetic capacity, dietary protein intake, and diet adherence.

Dosage Adjustment and Monitoring:

- Follow plasma ammonia levels to determine the need for dosage titration. (2.4)

Dosage Modifications in Patients with Hepatic Impairment:

- Start dosage at lower end of range. (2.5, 8.7)

DOSAGE FORMS AND STRENGTHS

Oral liquid: 1.1 g/mL. (3)

CONTRAINDICATIONS

Known hypersensitivity to phenylbutyrate. (4)

WARNINGS AND PRECAUTIONS

- Neurotoxicity: Phenylacetate (PAA), the active moiety of RAVICTI, may be toxic; reduce dosage for symptoms of neurotoxicity. (5.1)
- Pancreatic Insufficiency or Intestinal Malabsorption: Monitor ammonia levels closely. (5.2)

ADVERSE REACTIONS

Most common adverse reactions (≥10%) in adults are: diarrhea, flatulence, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Horizon Therapeutics at 1-855-823-7878 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Corticosteroids, valproic acid, or haloperidol: May increase plasma ammonia level; monitor ammonia levels closely. (7.1)
- Probenecid: May affect renal excretion of metabolites of RAVICTI, including phenylacetylglutamine (PAGN) and PAA. (7.2)
- CYP3A4 Substrates with narrow therapeutic index (e.g., alfentanil, quinidine, cyclosporine): RAVICTI may decrease exposure; monitor for decreased efficacy of the narrow therapeutic index drug. (7.3)
- Midazolam: Decreased exposure; monitor for suboptimal effect of midazolam. (7.3)

USE IN SPECIFIC POPULATIONS

Lactation: Breastfeeding is not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

RAVICTI is indicated for use as a nitrogen-binding agent for chronic management of patients with urea cycle disorders (UCDs) who cannot be managed by dietary protein restriction and/or amino acid supplementation alone. RAVICTI must be used with dietary protein restriction and, in some cases, dietary supplements (e.g., essential amino acids, arginine, citrulline, protein-free calorie supplements).

Limitations of Use:

- RAVICTI is not indicated for the treatment of acute hyperammonemia in patients with UCDs because more rapidly acting interventions are essential to reduce plasma ammonia levels.
- The safety and efficacy of RAVICTI for the treatment of *N*-acetylglutamate synthase (NAGS) deficiency has not been established.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

RAVICTI should be prescribed by a physician experienced in the management of UCDs.

- Instruct patients to take RAVICTI with food or formula and to administer directly into the mouth via oral syringe or dosing cup.
- Instruct that RAVICTI should be administered just prior to breastfeeding in infants who are breastfeeding.
- For patients who cannot swallow, see the instructions on administration of RAVICTI by nasogastric tube or gastrostomy tube *[see Dosage and Administration (2.6)]*.
- For patients who require a volume of less than 1 mL per dose via nasogastric or gastrostomy tube, the delivered dose may be less than anticipated. Closely monitor these patients using ammonia levels *[see Dosage and Administration (2.6)]*.
- The recommended dosages for patients switching from sodium phenylbutyrate to RAVICTI and patients naïve to phenylbutyric acid are different *[see Dosage and Administration (2.2, 2.3)]*. For both subpopulations:
  - Patients 2 years of age and older: Give RAVICTI in 3 equally divided dosages, each rounded up to the nearest 0.5 mL
  - Patients less than 2 years: Give RAVICTI in 3 or more equally divided dosages, each rounded up to the nearest 0.1 mL.
  - The maximum total daily dosage is 17.5 mL (19 g).

- RAVICTI must be used with dietary protein restriction and, in some cases, dietary supplements (e.g., essential amino acids, arginine, citrulline, protein-free calorie supplements).

2.2 Switching From Sodium Phenylbutyrate to RAVICTI

Patients switching from sodium phenylbutyrate to RAVICTI should receive the dosage of RAVICTI that contains the same amount of phenylbutyric acid. The conversion is as follows:

Total daily dosage of RAVICTI (mL) = total daily dosage of sodium phenylbutyrate tablets (g) x 0.86

Total daily dosage of RAVICTI (mL) = total daily dosage of sodium phenylbutyrate powder (g) x 0.81

2.3 Initial Dosage in Phenylbutyrate-Naïve Patients

The recommended dosage range, based upon body surface area, in patients naïve to phenylbutyrate (PBA) is 4.5 to 11.2 mL/m^2/day (5 to 12.4 g/m^2/day). For patients with some residual enzyme activity who are not adequately controlled with protein restriction, the recommended starting dosage is 4.5 mL/m^2/day.

In determining the starting dosage of RAVICTI in treatment-naïve patients, consider the patient's residual urea synthetic capacity, dietary protein requirements, and diet adherence. Dietary protein is approximately 16% nitrogen by weight. Given that approximately 47% of dietary nitrogen is excreted as waste and approximately 70% of an administered PBA dose will be converted to urinary phenylacetylglutamine (U-PAGN), an initial estimated RAVICTI dose for a 24-hour period is 0.6 mL RAVICTI per gram of dietary protein ingested per 24-hour period. The total daily dosage should not exceed 17.5 mL.

2.4 Dosage Adjustment and Monitoring

During treatment with RAVICTI, patients should be followed clinically and with plasma ammonia levels to determine the need for dosage titration. Closely monitor plasma ammonia levels during treatment with RAVICTI and when changing the dosage of RAVICTI.

The methods used for measuring plasma ammonia levels vary among individual laboratories and values obtained using different assay methods may not be interchangeable. Normal ranges and therapeutic target levels for plasma ammonia depend upon the assay method used by the individual laboratory. During treatment with RAVICTI, refer to the assay-specific normal ranges and to the therapeutic target ranges for plasma ammonia.

Normal Plasma Ammonia

In patients treated with RAVICTI who experience neurologic symptoms (e.g. nausea, vomiting, headache, somnolence or confusion) in the absence of high plasma ammonia or other intercurrent illness to explain these symptoms, consider reducing the RAVICTI dosage and clinically monitor patients for potential neurotoxicity from high phenylacetate (PAA) concentrations. If available, obtain measurements of plasma PAA concentrations and plasma phenylacetylglutamine (PAGN) to calculate the ratio of plasma PAA to PAGN which may help to guide RAVICTI dosing. The PAA to PAGN ratio has generally been less than 1 in patients with UCDs who did not have significant plasma PAA accumulation. In general, a high PAA to PAGN ratio may indicate a slower or less efficient conjugation reaction to form

PAGN, which may lead to increases in PAA without further conversion to PAGN *[see Warnings and Precautions (5.1), Clinical Pharmacology (12.3)]*.

Elevated Plasma Ammonia

In patients 6 years and older, when plasma ammonia is elevated, increase the RAVICTI dosage to maintain fasting plasma ammonia to less than half the upper limit of normal (ULN). In infants and pediatric patients below 6 years of age, if obtaining fasting ammonia is problematic due to frequent feedings, adjust the RAVICTI dosage to keep the first ammonia of the morning below the ULN for age. If available, the ratio of PAA to PAGN in the same plasma sample may provide additional information to assist in dosage adjustment decisions *[see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]*.

Dietary Protein Intake

If available, urinary phenylacetylglutamine (U-PAGN) measurements may be used to help guide RAVICTI dosage adjustment. Each gram of U-PAGN excreted over 24 hours covers waste nitrogen generated from 1.4 grams of dietary protein. If U-PAGN excretion is insufficient to cover daily dietary protein intake and the fasting ammonia is greater than half the ULN, the RAVICTI dosage should be increased. The amount of dosage adjustment should factor in the amount of dietary protein that has not been covered, as indicated by the 24-hour U-PAGN output, and the estimated RAVICTI dose needed per gram of dietary protein ingested and the maximum total daily dosage (i.e., 17.5 mL).

Consider a patient's use of concomitant medications, such as probenecid, when making dosage adjustment decisions based on U-PAGN. Probenecid may result in a decrease of the urinary excretion of PAGN *[see Drug Interactions (7.2)]*.

2.5 Dosage Modifications in Patients with Hepatic Impairment

For patients with moderate to severe hepatic impairment, the recommended starting dosage is at the lower end of the recommended dosing range (4.5 mL/m^2/day) and the dosage should be kept at the lowest necessary to control the patient's plasma ammonia *[see Use in Specific Populations (8.7)]*.

2.6 Preparation for Nasogastric Tube or Gastrostomy Tube Administration

It is recommended that all patients who can swallow take RAVICTI orally, even those with nasogastric and/or gastrostomy tubes. However, for patients who cannot swallow, a nasogastric tube or gastrostomy tube may be used to administer RAVICTI as follows:

- Utilize an oral syringe to withdraw the prescribed dosage of RAVICTI from the bottle.
- Place the tip of the syringe into the nasogastric/gastrostomy tube.
- Utilizing the plunger of the syringe, administer RAVICTI into the tube.
- Flush once with 10 mL of water or formula and allow the flush to drain.

- If needed, flush a second time with an additional 10 mL of water or formula to clear the tube.

For patients who require a volume of less than 1 mL per dose via nasogastric or gastrostomy tube, the delivered dosage may be less than anticipated due to adherence of RAVICTI to the plastic tubing. Therefore, these patients should be closely monitored using ammonia levels following initiation of RAVICTI dosing or dosage adjustments.

3 DOSAGE FORMS AND STRENGTHS

Oral liquid: colorless to pale yellow, 1.1 g/mL of glycerol phenylbutyrate (delivers 1.02 g/mL of phenylbutyrate).

4 CONTRAINDICATIONS

RAVICTI is contraindicated in patients with known hypersensitivity to phenylbutyrate. Signs of hypersensitivity include wheezing, dyspnea, coughing, hypotension, flushing, nausea, and rash.

5 WARNINGS AND PRECAUTIONS

5.1 Neurotoxicity

Increased exposure to PAA, the major metabolite of RAVICTI, may be associated with neurotoxicity in patients with UCDs. In a study of adult cancer patients, subjects received sodium phenylacetate administered as a 1-hour infusion twice daily at two dose levels of 125 and 150 mg/kg for a 2-week period. Of 18 subjects enrolled, 7 had a history of primary central nervous system tumor. Signs and symptoms of potential PAA neurotoxicity, which were reversible, were reported at plasma PAA concentrations above 500 micrograms/mL and included somnolence, fatigue, lightheadedness, headache, dysgeusia, hypoacusis, disorientation, impaired memory, and exacerbation of preexisting neuropathy. PAA concentrations were not measured when symptoms resolved.

In healthy subjects, after administration of 4 mL and 6 mL RAVICTI 3 times daily (13.2 g/day and 19.8 g/day, respectively) for 3 days, a dose-dependent increase in non-serious nervous system adverse reactions were observed. In subjects who had nervous system adverse reactions, plasma PAA concentrations, which were measured on Day 3 per protocol and not always at onset of symptoms, ranged from 8 to 56 micrograms/mL with 4 mL RAVICTI 3 times daily and from 31 to 242 micrograms/mL with 6 mL RAVICTI 3 times daily.

In clinical trials in patients with UCDs who had been on sodium phenylbutyrate prior to administration of RAVICTI, adverse reactions of headache, fatigue, symptoms of peripheral neuropathy, seizures, tremor and/or dizziness were reported. No correlation between plasma PAA concentration and neurologic symptoms was identified but plasma PAA concentrations were generally not consistently measured at the time of neurologic symptom occurrence *[see Clinical Pharmacology (12.3)]*.

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