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)	04/2017
Dosage and Administration (2.1)	04/2017
Dosage and Administration (2.2)	04/2017

INDICATIONS AND USAGE

RAVICTI is a nitrogen-binding agent indicated for chronic management of patients 2 months of age and older 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, 8.6)

DOSAGE FORMS AND STRENGTHS

Oral liquid: 1.1 g/mL. (3)

CONTRAINDICATIONS

- Patients less than 2 months of age. (4)
- 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)
- Reduced Phenylbutyrate Absorption in 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: 04/2017

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 2 months of age and older 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.
- 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 2 months of age to 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 ammonia levels after changing the dosage of RAVICTI.

Normal Ammonia Levels

If patients experience symptoms of vomiting, nausea, headache, somnolence or confusion in the absence of high ammonia levels or other intercurrent illnesses, reduce the RAVICTI dosage and monitor patients clinically. If available, obtain measurements of plasma phenylacetate (PAA) concentrations and the ratio of plasma PAA to PAGN to guide dosing. A high PAA to PAGN ratio may indicate the saturation of the conjugation reaction to form PAGN. The PAA to PAGN ratio has been observed to be generally less than 1 in patients with UCDs without significant PAA accumulation *[see Warnings and Precautions (5.1), Clinical Pharmacology (12.3)]*.

Elevated Ammonia Levels

When plasma ammonia is elevated, increase the RAVICTI dosage to reduce the fasting ammonia level to less than half the upper limit of normal (ULN) in patients 6 years and older. In infants and pediatric patients (generally below 6 years of age), where obtaining fasting ammonia is problematic due to frequent feedings, adjust the dosage to keep the first ammonia of the morning below the ULN.

Urinary Phenylacetylglutamine: If available, 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 adjusted upward. 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 level 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)]*.

Plasma Phenylacetate and Phenylacetylglutamine: If available, the ratio of PAA to PAGN in plasma may provide additional information to assist in dosage adjustment decisions. In patients with a high PAA to PAGN ratio, a further increase in RAVICTI dosage may not increase PAGN formation, even if plasma PAA concentrations are increased, due to saturation of the conjugation reaction *[see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]*.

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 kept at the lowest dose necessary to control the patient's ammonia levels *[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

- Less than 2 months of age. Pediatric patients less than 2 months of age may have immature pancreatic exocrine function, which could impair hydrolysis of RAVICTI, leading to impaired absorption of phenylbutyrate and hyperammonemia *[see Use in Specific Populations (8.4)]*.
- With known hypersensitivity to phenylbutyrate. Signs of hypersensitivity include wheezing, dyspnea, coughing, hypotension, flushing, nausea, and rash.

5 WARNINGS AND PRECAUTIONS

5.1 Neurotoxicity

The major metabolite of RAVICTI, PAA, is associated with neurotoxicity. Signs and symptoms of PAA neurotoxicity, including somnolence, fatigue, lightheadedness, headache, dysgeusia, hypoacusis, disorientation, impaired memory, and exacerbation of preexisting neuropathy, were observed at plasma PAA concentrations of 500 micrograms/mL in a study of adult cancer patients who were administered PAA intravenously. In this study, adverse reactions were reversible.

In healthy subjects, after administration of 4 mL and 6 mL RAVICTI 3 times daily for 3 days, a dose-dependent increase in all-grade nervous system adverse reactions was observed, even at exposure levels of PAA less than 100 micrograms/mL.

In clinical trials in patients with UCDs who had been on sodium phenylbutyrate prior to administration of RAVICTI, peak PAA concentrations after dosing with RAVICTI ranged from 1.6 to 178 micrograms/mL (mean: 39 micrograms/mL) in adult patients, from 1 to 410 micrograms/mL (mean: 70 micrograms/mL; median: 50 micrograms/mL) in pediatric patients ages 2 years and older, and from 1 to 1215 micrograms/mL (mean: 142 micrograms/mL; median: 35 micrograms/mL) in pediatric patients ages 2 months to less than 2 years. Some patients with UCDs experienced headache, fatigue, symptoms of peripheral neuropathy, seizures, tremor and/or dizziness. No correlation between PAA levels and neurotoxicity symptoms was identified but PAA levels were generally not measured at the time of neurotoxicity symptoms.

If symptoms of vomiting, nausea, headache, somnolence or confusion, are present in the absence of high ammonia or other intercurrent illnesses, reduce the RAVICTI dosage *[see Dosage and Administration (2.4)]*.

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