CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203284Orig1s000

LABELING

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

INDICATIONS AND USAGE

RAVICTI is indicated for use as a nitrogen-binding agent for chronic management of adult and pediatric patients ≥2 years of age with urea cycle disorders (UCDs) that 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 (eg, essential amino acids, arginine, citrulline, protein-free calorie 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)
- The use of RAVICTI in patients <2 months of age is contraindicated (4)

DOSAGE AND ADMINISTRATION

RAVICTI should be prescribed by a physician experienced in management of UCDs. (2.1)

- Instruct patients to take with food and to administer directly into mouth via oral syringe or dosing cup. (2.1)
- Total daily dosage is given in 3 equally divided dosages, rounded up to nearest 0.5 mL. (2.1)
- Maximum daily dosage is 17.5 mL (19 g). (2.1)
- Must be used with dietary protein restriction. (2.1)

Switching From Sodium Phenylbutyrate to RAVICTI:

- Daily dosage of RAVICTI (mL) = daily dosage of sodium phenylbutyrate (g) x 0.86. (2.2)

Initial Dosage in Phenylbutyrate-Naïve Patients:

- Recommended dosage range is 4.5 to 11.2 mL/m^2/day (5 to 12.4 g/m^2/day). (2.3)
- For patients with some residual enzyme activity who are not adequately controlled with dietary restriction, recommended starting dose is 4.5 mL/m^2/day. (2.3)
- Take into account patient's estimated urea synthetic capacity, dietary protein intake, and diet adherence. (2.3)

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 of glycerol phenylbutyrate. (3)

CONTRAINDICATIONS

- Patients <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 in ≥10% of patients are diarrhea, flatulence, and headache. (6)
To report SUSPECTED ADVERSE REACTIONS, contact Hyperion 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 PAGN and PAA. (7.2)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Nursing Mothers: Discontinue nursing or discontinue the drug. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: January 2013

FULL PRESCRIBING INFORMATION: CONTENTS*

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

1 INDICATIONS AND USAGE

RAVICTI is indicated for use as a nitrogen-binding agent for chronic management of adult and pediatric patients ≥2 years of age 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 (eg, 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.

The use of RAVICTI in patients <2 months of age is contraindicated [see *Contraindications (4)*].

2 DOSAGE AND ADMINISTRATION

2.1 Important Instructions

RAVICTI should be prescribed by a physician experienced in the management of UCDs. Instruct patients to take RAVICTI with food and to administer directly into the mouth via oral syringe or dosing cup. See the instructions on the use of RAVICTI by nasogastric tube or g-tube [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:

- Give RAVICTI in 3 equally divided dosages, each rounded up to the nearest 0.5 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 (g) x 0.8

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

Adjustment based on Plasma Ammonia: Adjust the RAVICTI dosage to produce a fasting plasma ammonia level that is less than half the upper limit of normal (ULN) according to age.

Adjustment Based on Urinary Phenylacetylglutamine: If available, U-PAGN measurements may be used to help guide RAVICTI dose 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 dose should be adjusted upward. The amount of dose adjustment should factor in the amount of dietary protein that has not been covered, as indicated by the 24-h 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)*].

Adjustment Based on Plasma Phenylacetate: If available, measurements of the plasma PAA levels may be useful to guide dosing if symptoms of vomiting, nausea, headache, somnolence, confusion, or sleepiness are present in the absence of high ammonia or intercurrent illness. Ammonia levels must be monitored closely when changing the dose of RAVICTI. The ratio of PAA to PAGN in plasma may provide additional information to assist in dose adjustment decisions. In patients with a high PAA to PAGN ratio, a further increase in RAVICTI dose may not increase PAGN formation, even if plasma PAA concentrations are increased, due to saturation of the conjugation reaction. The PAA to PAGN ratio has been observed to be generally less than 1 in patients without significant PAA accumulation. [see *Warnings and Precautions (5.1)*].

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 range [see *Warnings and Precautions (5.1)* and *Hepatic Impairment (8.6)*].

2.6 Preparation for Nasogastric Tube or Gastrostomy Tube Administration

For patients who have a nasogastric tube or gastrostomy tube in place, 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 to the tip of the gastrostomy/nasogastric tube.
- Utilizing the plunger of the syringe, administer RAVICTI into the tube.
- Flush once with 30 mL of water and allow the flush to drain.
- Flush a second time with an additional 30 mL of water to clear the tube.

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. Children <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 *Pediatric Use (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 ≥500 µg/mL in a study of cancer patients who were administered IV PAA. In this study, adverse events 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 <100 µg/mL.

In clinical trials in UCD patients who had been on sodium phenylbutyrate prior to administration of RAVICTI, peak PAA concentrations after dosing with RAVICTI ranged from 1.6 to 178 µg/mL (mean: 39 µg/mL) in adult patients and from 7 to 480 µg/mL (mean: 90 µg/mL) in pediatric patients. Some UCD patients experienced headache, fatigue,

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