MEDICATION GUIDE
RAVICTI (rah-VIK- tee)
(glycerol phenylbutyrate)
oral liquid

What is the most important information I should know about RAVICTI?
RAVICTI may cause serious side effects, including:
Nervous system problems (Neurotoxicity). Phenylacetate (PAA), a breakdown product of RAVICTI, may cause nervous system side effects. Call your doctor or get medical help right away if you get any of these symptoms while taking RAVICTI:

- sleepiness
- lightheadedness
- change in taste
- problems with hearing
- confusion
- problems with memory
- worsening of numbness, tingling, or burning in your hands or feet
- headache
- feeling very tired (fatigue)
- nausea
- vomiting

Your doctor may do blood tests to measure the amount of PAA in your blood during your treatment with RAVICTI.

What is RAVICTI?

- RAVICTI is a prescription medicine used in adults and in children 2 months of age and older for long-term management of high blood levels of ammonia (hyperammonemia) caused by a condition called a urea cycle disorder (UCD). RAVICTI should be used if the UCD cannot be managed with a low protein diet and dietary supplements alone. RAVICTI must be used along with a low protein diet and in some cases dietary supplements.
- RAVICTI is not used for the acute treatment of hyperammonemia in people with UCD.
- It is not known if RAVICTI is safe and effective for the treatment of N-acetylglutamate synthase (NAGS) deficiency.

Who should not take RAVICTI?

- Children less than 2 months of age should not take RAVICTI because it may not be digested in children less than 2 months of age.
- Do not take RAVICTI if you are allergic to phenylbutyrate. Call your doctor or go to the nearest hospital emergency room if you have wheezing, shortness of breath, cough, low blood pressure, flushing, nausea or a rash while taking RAVICTI.

Before taking RAVICTI, tell your doctor about any medical conditions and if you:

- Have liver or kidney problems.
- Have pancreas or bowel (intestine) problems.
- Are pregnant or plan to become pregnant. It is not known if RAVICTI will harm your unborn baby.
- **Pregnancy Registry**: There is a Pregnancy Registry for women who take RAVICTI just before becoming pregnant or who become pregnant during treatment with RAVICTI. The purpose of this registry is to collect information about the health of you and your baby. Talk to your doctor about how you can join the Pregnancy Registry. For more information about this registry, call 1-855-823-2595 or visit www.ucdregistry.com.
- Are breastfeeding or plan to breastfeed. It is not known if RAVICTI passes into your breast milk. Breastfeeding is not recommended during treatment with RAVICTI. Talk to your doctor about the best way to feed your baby if you take RAVICTI.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, dietary and herbal supplements.
Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take RAVICTI?

- Take RAVICTI exactly as your doctor tells you.
- Your doctor will tell you how much RAVICTI to take and when to take it.
- Your doctor may change your dose if needed.
- Take RAVICTI with food or formula.
- RAVICTI is an oral liquid that is taken by mouth using an oral syringe or dosing cup. Ask your pharmacist for an oral syringe or dosing cup if you do not have one.
- If you have a nasogastric or gastrostomy tube in place and can swallow, you should take RAVICTI by mouth.
- Stay on the diet that your doctor gives you.
- If you take too much RAVICTI, call your doctor or your poison control center at 1-800-222-1222 or go to the nearest hospital emergency room right away.

For people who cannot swallow and who have a nasogastric or gastrostomy tube in place, RAVICTI should be given as follows:

- Use an oral syringe to withdraw the prescribed dose of RAVICTI from the bottle.
- Place the tip of the syringe into the nasogastric or gastrostomy tube and push the plunger of the syringe to give RAVICTI into the tube.
- Add 10 mL of water or formula to the syringe and push the plunger of the syringe to flush any remaining medicine

from the nasogastric or gastrostomy tube into the stomach.
- If needed, flush the nasogastric or gastrostomy tube again with 10 mL of water or formula to clear the nasogastric or gastrostomy tube.

What are the possible side effects of RAVICTI?

RAVICTI may cause serious side effects, including:

- See "**What is the most important information I should know about RAVICTI?**"

The most common side effects of RAVICTI in adults include:

- diarrhea
- gas
- headache
- abdomen (stomach) pain
- vomiting
- tiredness
- decreased appetite
- indigestion or heartburn

The most common side effects of RAVICTI in children 2 years to 17 years of age include:

- upper abdomen (stomach) pain
- rash
- nausea
- vomiting
- diarrhea
- decreased appetite
- headache

The most common side effects of RAVICTI in children 2 months to less than 2 years of age include:

- low white blood cell count (neutropenia)
- vomiting
- diarrhea
- fever
- reduced food intake
- cough
- stuffy nose
- runny nose
- skin rash
- small round bumps on the skin

Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all of the possible side effects of RAVICTI.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store RAVICTI?

- Store RAVICTI between 68ºF to 77ºF (20°C to 25°C).

Keep RAVICTI and all medicines out of the reach of children.

General information about the safe and effective use of RAVICTI.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use RAVICTI for a condition for which it was not prescribed. Do not give RAVICTI to other people, even if they have the same symptoms you have. It may harm them.

You can ask your doctor or pharmacist for information about RAVICTI that is written for health professionals.

What are the ingredients in RAVICTI?

Active ingredient: glycerol phenylbutyrate

Distributed by: Horizon Pharma USA, Inc., Lake Forest, IL 60045.

For more information, go to www.RAVICTI.com or call 1-855-823-7878.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 04/2017

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

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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

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