Assess how your patients are doing on RAVICTI® (glycerol phenylbutyrate) Oral Liquid.

Use this guide to assess management of urea cycle disorders (UCDs) for patients who have recently transitioned to RAVICTI. Have an open dialogue around the importance of targeting ammonia control with appropriate dosing and administration of RAVICTI, the use of consistent testing, and tools for patient-specific support.

CHECK AMMONIA LEVELS AND OTHER BIOMARKERS

☐ **Follow recommended practices for assessing plasma ammonia and glutamine.[1]**

- Ensure that monitoring of ammonia occurs regularly.[1]
- Measure fasting ammonia, which is related to daily ammonia exposure and hyperammonemic crises.[2]
- 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.[3]
    - 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.[3]
- Monitor glutamine levels along with other plasma amino acids.[1,a]

[a]Mean glutamine levels during RAVICTI clinical trials were similar at baseline (763 µmol/L) and month 12 (748 µmol/L) and remained within normal range (less than 1000 µmol/L) throughout the 12-month period. Normal values may vary between different laboratories due to variations in methods and specimen types.[1,4]

☐ **Consider ordering phenylbutyrate metabolite testing to optimize RAVICTI dosage.[5,6]**

- Order Phenylbutyrate Metabolite Analysis kits online at **https://www.ravictihcp.com/order-kit**.
- Testing kits are available through Baylor Genetics at no charge to you or your patient.

ASK ABOUT THE PROGRESS OF YOUR PATIENT'S TRANSITION

☐ **Assess whether the transition to RAVICTI went as planned.**

☐ **Inquire about any perceived changes since transitioning to RAVICTI.**

☐ **Identify any patient concerns with their ammonia control and dietary requirements.**

☐ **Remind patients that treatment optimization is an ongoing process, and communication with the care team is essential.**

INDICATION

RAVICTI® (glycerol phenylbutyrate) Oral Liquid 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 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.

Please review the RAVICTI Important Safety Information on page 3 and the Full Prescribing Information here.

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Rethink potential.

REINFORCE PROPER ADMINISTRATION TECHNIQUES

☐ **Underscore how to administer RAVICTI® (glycerol phenylbutyrate) Oral Liquid.**

- Discuss taking RAVICTI with meals or formula; for infants who are breastfed, RAVICTI should be administered just prior to breastfeeding.[3]
- Discuss proper flushing of nasogastric or gastrostomy tube.[3]

☐ **Refer patient to RAVICTI Instructions for Use included in the RAVICTI Patient Starter Kit.**

☐ **Review RAVICTI administration videos with the patient; videos can be accessed online at https://www.ravictiHCP.com.**

INTRODUCE SUPPORT PROGRAMS TO PATIENTS

☐ **Horizon Patient Services**

- The Horizon Patient Services program is dedicated to improving the lives of people living with UCDs. The program provides ongoing individualized support and education for your patients and their families.
- Direct patients to learn more online or by telephone:
  - Go to **https://ravicti.com/urea-cycle-disorder-patient-support**.
  - Call 1-855-UCD-SUPT (1-855-823-7878), Monday through Friday, 9 AM to 8 PM (EST).

☐ **UCD Mentors**

- The UCD Mentors are patients and caregivers who understand what it's like to live with a UCD. Patients can watch a video online, choose a mentor, and schedule a call.
- Direct patients and their caregivers to learn more online at **https://www.ravicti.com/meet-mentors/**.

Please review the RAVICTI Important Safety Information on page 3 and the Full Prescribing Information here.

References: **1.** Häberle J, Boddaert N, Burlina A, et al. Suggested guidelines for the diagnosis and management of urea cycle disorders. *Orphanet J Rare Dis.* 2012;7:32. doi:10.1186/1750-1172-7-32. **2.** Lee B, Diaz GA, Rhead W, et al. Blood ammonia and glutamine as predictors of hyperammonemic crises in patients with urea cycle disorder. *Genet Med.* 2015;17(7):561-568. doi:10.1038/gim.2014.148. **3.** RAVICTI (glycerol phenylbutyrate) Oral Liquid [prescribing information] Horizon. **4.** Longo N, Holt RJ. Glycerol phenylbutyrate for the maintenance treatment of patients with deficiencies in enzymes of the urea cycle. *Exp Opin Orphan Drug.* 2017;12(5):999-1010. doi:10.1080/21678707.2017.1405807. **5.** Mokhtarani M, Diaz GA, Rhead W, et al. Urinary phenylacetylglutamine as dosing biomarker for patients with urea cycle disorders. *Mol Genet Metab.* 2012;107(3):308-314. doi:10.1016/j.ymgme.2012.08.006. **6.** Mokhtarani M, Diaz GA, Rhead W, et al. Elevated phenylacetic acid levels do not correlate with adverse events in patients with urea cycle disorders or hepatic encephalopathy and can be predicted based on the plasma PAA to PAGN ratio. *Mol Genet Metab.* 2013;110(4):446-453. doi:10.1016/j.ymgme.2013.09.017.

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INDICATION and IMPORTANT SAFETY INFORMATION

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IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- *Patients with known hypersensitivity to phenylbutyrate:* Reactions include wheezing, dyspnea, coughing, hypotension, flushing, nausea, and rash.

WARNINGS AND PRECAUTIONS

- *Neurotoxicity:* Phenylacetate (PAA), the major metabolite of RAVICTI, may be toxic at levels of 500 micrograms/mL or greater. If symptoms of vomiting, nausea, headache, somnolence, or confusion, are present in the absence of high ammonia or other intercurrent illness which explains these symptoms, consider the potential for PAA neurotoxicity which may need reduction in the RAVICTI dosage.
- *Pancreatic Insufficiency or Intestinal Malabsorption:* Low or absent pancreatic enzymes or intestinal disease resulting in fat malabsorption may result in reduced or absent digestion of RAVICTI and/or absorption of phenylbutyrate and reduced control of plasma ammonia. Monitor ammonia levels closely.

ADVERSE REACTIONS

The most common adverse reactions reported in clinical trials (at least 10% of patients) were:

- *Adult patients:* diarrhea, flatulence, and headache occurred during 4-week treatment (n=45) with RAVICTI; nausea, vomiting, diarrhea, decreased appetite, dizziness, headache, and fatigue occurred during 12-month treatment (n=51) with RAVICTI.
- *Pediatric patients ages 2 to 17 years:* upper abdominal pain, rash, nausea, vomiting, diarrhea, decreased appetite, and headache occurred during 12-month treatment (n=26) with RAVICTI.
- *Pediatric patients ages 2 months to less than 2 years:* neutropenia, vomiting, constipation, diarrhea, pyrexia, hypophagia, cough, nasal congestion, rhinorrhea, rash, and papule occurred during 12-month treatment (n=17) with RAVICTI.
- *Pediatric patients less than 2 months of age:* vomiting, rash, gastroesophageal reflux, increased hepatic enzymes, feeding disorder (decreased appetite, hypophagia), anemia, cough, dehydration, metabolic acidosis, thrombocytosis, thrombocytopenia, neutropenia, lymphocytosis, diarrhea, flatulence, constipation, pyrexia, lethargy, and irritability/agitation occurred during 24-month treatment (n=16) with RAVICTI.

DRUG INTERACTIONS

- Corticosteroids, valproic acid, or haloperidol may increase plasma ammonia level. Monitor ammonia levels closely.
- Probenecid may affect renal excretion of metabolites of RAVICTI, including phenylacetylglutamine (PAGN) and PAA.
- CYP3A4 substrates with narrow therapeutic index (eg, alfentanil, quinidine, cyclosporine): RAVICTI may decrease exposure to the concomitant drug.
- Midazolam: Use of RAVICTI decreased exposure of midazolam with concomitant use.

USE IN SPECIFIC POPULATIONS

- *Pregnancy:* RAVICTI should be used with caution in patients who are pregnant or planning to become pregnant. Based on animal data, RAVICTI may cause fetal harm. A voluntary patient registry monitors pregnancy outcomes in women exposed to RAVICTI. For more information regarding the registry program, visit www.ucdregistry.com or call 1-855-823-2595.
- *Lactation:* breastfeeding is not recommended during treatment with RAVICTI. There are no data on the presence of RAVICTI in human milk, the effects on the breastfed infant, nor the effects on milk production.

Please see Full Prescribing Information here.

HORIZON

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