USING THE FULL CLINICAL PICTURE TO Optimize RAVICTI® (glycerol phenylbutyrate) Oral Liquid Dose

DOSING FUNDAMENTALS

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 (eg, essential amino acids, arginine, citrulline, protein-free calorie supplements).

Scan or click **here** to use the **RAVICTI dosing calculator**.

DOSAGE[a]

The recommended RAVICTI dosage range in patients naïve[b] to phenylbutyrate is **4.5 to 11.2 mL/m²/day (5 to 12.4 g/m²/day)**.[c,d] These values are multiplied by the patient's BSA to calculate the daily dosage range[1,b]

The maximum total daily dosage is **17.5 mL (19 g)**

The total daily dosage of RAVICTI should be **divided into equal doses** based on age

- Patients 2+ years of age: 3 equally divided doses, each rounded up to the nearest 0.5 mL
- Patients less than 2 years of age: 3 or more equally divided doses, each rounded up to the nearest 0.1 mL

See nasogastric tube or G-tube administration instructions (Section 2.6 of Full Prescribing Information)

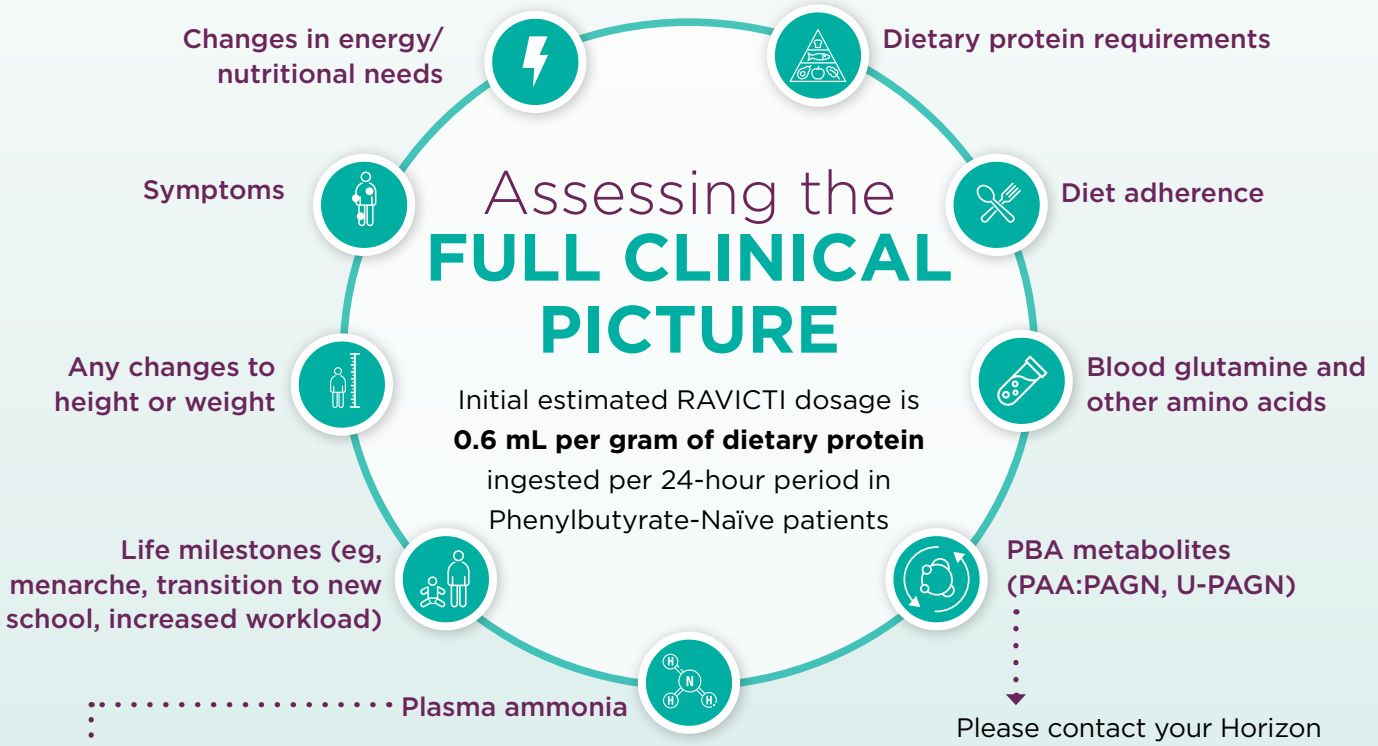
[a]See **Full Prescribing Information**.
[b]Patients switching from sodium phenylbutyrate to RAVICTI should receive the dosage of RAVICTI that contains the same amount of phenylbutyric acid. See Section 2.2 of the full prescribing information for conversion.
[c]For patients with some residual enzyme activity who are not adequately controlled with protein restriction, the recommended starting dosage is 4.5 mL/m²/day.
[d]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/m²/day) and the dosage should be kept at the lowest necessary to control the patient's plasma ammonia.

BSA, body surface area; FDA, US Food and Drug Administration; G-tube, gastrostomy tube.

SELECT IMPORTANT SAFETY INFORMATION—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.

Assessing the full clinical picture allows modification of RAVICTI® (glycerol phenylbutyrate) Oral Liquid dosing for targeted ammonia control.[1,2]



- When plasma ammonia is elevated in patients ≥6 years of age, increase the RAVICTI dosage to maintain fasting plasma ammonia to less than half the ULN
- In infants and children <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[1]; if available, the ratio of PAA to PAGN in the same plasma sample may provide additional information to assist in dosage adjustment decisions
- Closely monitor ammonia levels of patients who require <1 mL per dose via nasogastric or G-tube; the delivered dose may be less than anticipated due to RAVICTI adhering to the plastic tubing[1]

Please contact your Horizon representative or visit www.RAVICTIHCP.com by scanning or clicking **here** to learn more about **PBA metabolite testing** and to order no-cost metabolite testing kits.

G-tube, gastrostomy tube; PAA, phenylacetate; PAGN, phenylacetylglutamine; PBA, phenylbutyrate; U, urinary; ULN, upper limit of normal.

SELECT IMPORTANT SAFETY INFORMATION—CONTRAINDICATIONS

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

QUESTIONS TO ASK YOUR PATIENTS

Advise your patients to read the FDA-approved patient labeling (Medication Guide) and discuss Patient Counseling Information (Section 17 of Full Prescribing Information).

It is also important to discuss with your patients how they plan to take their RAVICTI® (glycerol phenylbutyrate) Oral Liquid when they are on the go.

How will you store your RAVICTI until it's time for your next dose?

What time will you take each dose?

How will you remind yourself to take your dose on schedule?

How will you ensure you have taken all of your doses each day?

What will you do if you miss or forget a RAVICTI dose?

If you have any questions about RAVICTI dosing, please contact Horizon Therapeutics Medical Information at 1-866-479-6742.

SELECT IMPORTANT SAFETY INFORMATION—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.

INDICATION AND IMPORTANT SAFETY INFORMATION

Please see **Full Prescribing Information** by clicking **here**.

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.

IMPORTANT SAFETY INFORMATION CONTRAINDICATIONS

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WARNINGS AND PRECAUTIONS

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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. Report pregnancies to Horizon at 1-866-479-6742.
- *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.

REFERENCES

1. RAVICTI (glycerol phenylbutyrate) Oral Liquid [prescribing information] Horizon.
2. Stepien KM, Gerberhiwot T, Hendriksz CJ, Traecy EP. Challenges in diagnosing and managing adult patients with urea cycle disorders. *J Inherit Metab Dis*. 2005;42(6):1136-1146. doi: 10.1002/jimd.12096 .

Please see Full Prescribing Information by scanning or clicking **here**.

HORIZON. RAVICTI® (glycerol phenylbutyrate) Oral Liquid