How to dose RAVICTI® (glycerol phenylbutyrate) Oral Liquid

A REFERENCE GUIDE FOR DOSING, ADMINISTRATION, AND SUPPORT

> RAVICTI is easy to take...
> **It's just one little moment."**
>
> **Isaac,** Age 23
> Actual RAVICTI patient

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 10 and the BUPHENYL (sodium phenylbutyrate) Important Safety Information on page 11, and the accompanying Full Prescribing Information in pocket.

RAVICTI®
(glycerol phenylbutyrate) Oral Liquid
Rethink potential.

Get ready to start your patients on RAVICTI (glycerol phenylbutyrate) Oral Liquid

Whether your patients with UCDs are new to phenylbutyrate treatment or are switching from sodium phenylbutyrate, this brochure contains important information you need to start them on RAVICTI.

Inside, you will find:

- An easy-to-use tool to calculate the dosage of RAVICTI for patients who are switching from sodium phenylbutyrate tablets or powder
- Dosing information for patients who are naïve to phenylbutyrate treatment
- Guidelines for modifying the RAVICTI dosage for targeted ammonia control
- Administration reminders for patients and caregivers
- Important Safety Information

> "RAVICTI is the constant in your everyday life. **It just fits in.**"
>
> **Amy,** mother of a patient with a UCD

Updates and support

The following RAVICTI updates are highlighted in this brochure:

- RAVICTI is indicated for use as a nitrogen-binding agent for chronic management of adult and pediatric patients with UCDs who cannot be managed by dietary protein restriction and/or amino acid supplementation alone.[1]
- The total daily dosage of RAVICTI should be **divided into equal doses according to age range**.[1]
  - Patients 2 years of age and older: Give RAVICTI in 3 equally divided doses, each rounded up to the nearest 0.5 mL.[1]
  - Patients less than 2 years of age: Give RAVICTI in 3 or more equally divided doses, each rounded up to the nearest 0.1 mL.[1]

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

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.

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RAVICTI® (glycerol phenylbutyrate) Oral Liquid
Rethink potential.

RAVICTI: Effective ammonia control with easy dosing[1]

Your patients with UCDs need effective ammonia control. They also need a treatment formulation that fits into their lives. RAVICTI offers both.[1]

Consider the facts about RAVICTI:

- Easy-to-administer oral liquid[1]
- Nearly odorless and tasteless[2]
- No pill or powder preparation[1]
- Taken with meals or feedings via oral dosing syringe[1]
- Approved to treat all UCD subtypes except *N*-acetylglutamate synthase (NAGS) deficiency[1]

Remember, it is easy for your patients to make a full switch from sodium phenylbutyrate to RAVICTI without any gap or transition in treatment.[1]

Additional information

- Of 16 patients starting treatment at less than 2 months of age in a 24-month, open-label study, 5 patients (31%) reported a total of 7 hyperammonemic crises.[1]
- Of 17 pediatric patients 2 months to less than 2 years of age in 3 open-label studies, 7 patients (41%) reported a total of 11 hyperammonemic crises.[1]
- Of 26 pediatric patients 6 to 17 years of age in both 12-month studies of RAVICTI, 5 patients (19%) reported a total of 5 hyperammonemic crises.[1]
- Of 51 adult patients in the 12-month study of RAVICTI, 7 patients (14%) reported a total of 10 hyperammonemic crises.[1]

SELECT IMPORTANT SAFETY INFORMATION—CONTRAINDICATIONS

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

Please review the RAVICTI Important Safety Information on page 10 and the BUPHENYL® (sodium phenylbutyrate) Important Safety Information on page 11, and the accompanying Full Prescribing Information in pocket.

Get ready to start your patients on RAVICTI® (glycerol phenylbutyrate) Oral Liquid

Whether your patients with UCDs are new to phenylbutyrate treatment or are switching from sodium phenylbutyrate, this brochure contains important information you need to start them on RAVICTI.

Inside, you will find:

> "RAVICTI is the constant in your everyday life. **It just fits in.**"
>
> **Amy,** mother of a patient with a UCD

Updates and support

The following RAVICTI updates are highlighted in this brochure:

- RAVICTI is indicated for use as a nitrogen-binding agent for chronic management of adult and pediatric patients with UCDs who cannot be managed by dietary protein restriction and/or amino acid supplementation alone.[1]
- The total daily dosage of RAVICTI should be **divided into equal doses according to age range**.[1]
  - Patients 2 years of age and older: Give RAVICTI in 3 equally divided doses, each rounded up to the nearest 0.5 mL.[1]
  - Patients less than 2 years of age: Give RAVICTI in 3 or more equally divided doses, each rounded up to the nearest 0.1 mL.[1]

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

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.

Please review the RAVICTI Important Safety Information on page 10 and the BUPHENYL (sodium phenylbutyrate) Important Safety Information on page 11, and the accompanying Full Prescribing Information in pocket.

RAVICTI® (glycerol phenylbutyrate) Oral Liquid
Rethink potential.

SWITCHING TO RAVICTI

Switching from sodium phenylbutyrate to RAVICTI[1]

FROM TABLETS			FROM POWDER		
Total daily dosage of sodium phenylbutyrate tablets (g)[1]	Equals **total daily dosage** of RAVICTI (mL)[1]	Equals TID dose, properly rounded for selected age range[1,a]	Total daily dosage of sodium phenylbutyrate powder (g)[1]	Equals **total daily dosage** of RAVICTI (mL)[1]	Equals TID dose, properly rounded for selected age range[1]

To calculate the RAVICTI dosage, first choose which form of sodium phenylbutyrate you are converting. Confirm that the correct age range is showing above. Then pull the tab to convert the daily dosage of sodium phenylbutyrate to the recommended RAVICTI TID dose.

- This conversion ensures that patients switching from sodium phenylbutyrate to RAVICTI will receive the dosage that contains the same amount of phenylbutyric acid (PBA).[1]
- The total daily dosage of RAVICTI (mL) = total daily dosage of sodium phenylbutyrate tablets (g) x 0.86; when converting from sodium phenylbutyrate powder, multiply by 0.81.[1]
- To calculate more than 3 equally divided doses for patients less than 2 years of age, divide the calculated **total daily dosage** (center columns above) by the desired number of doses, and then round up to the nearest 0.1 mL.[1]

Remember, it is easy for your patients to make a full switch from sodium phenylbutyrate to RAVICTI without any gap or transition in treatment.[1]

Abbreviation: TID, 3 times per day.
[a]When converting 20 g of sodium phenylbutyrate tablets to RAVICTI for patients 2 years of age and older, the rounding of doses has been adjusted so that the total daily dosage does not exceed the maximum.[1]

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.

Please review the RAVICTI Important Safety Information on page 10 and the BUPHENYL (sodium phenylbutyrate) Important Safety Information on page 11, and the accompanying Full Prescribing Information in pocket.

Know the range and choose the starting dosage

4.5 mL/m²/day (5 g/m²/day) — **11.2 mL/m²/day** (12.4 g/m²/day) | **17.5 mL/day** (19 g/day)

THE RECOMMENDED DOSAGE RANGE FOR RAVICTI[1] | MAXIMUM DAILY DOSAGE[1]

- **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.[1]
- **For patients with moderate-to-severe hepatic impairment**, the recommended starting dosage is at the lower end of the range (4.5 mL/m²/day), and patients should be kept on the lowest dosage necessary to control ammonia levels.[1]

Additional considerations

Consider your patient's residual urea synthetic capacity, dietary protein requirements, and diet adherence. This information is important because the initial estimated RAVICTI dosage for a 24-hour period is 0.6 mL RAVICTI per gram of dietary protein ingested.[1,b]

Important reminders

- The total daily dosage of RAVICTI should be **divided into equal doses according to age range**.[1]
  - Patients 2 years of age and older: Give RAVICTI in 3 equally divided doses, each rounded up to the nearest 0.5 mL.[1]
  - Patients less than 2 years of age: Give RAVICTI in 3 or more equally divided doses, each rounded up to the nearest 0.1 mL.[1]
- The maximum total daily dosage is 17.5 mL (19 g).[1]
- 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]

[b]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 phenylbutyrate (PBA) dose will be converted to urinary phenylacetylglutamine (PAGN), an initial estimated RAVICTI dosage for a 24-hour period is 0.6 mL RAVICTI per gram of dietary protein ingested.[1]

SELECT IMPORTANT SAFETY INFORMATION—CONTRAINDICATIONS

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

Please review the RAVICTI Important Safety Information on page 10 and the BUPHENYL (sodium phenylbutyrate) Important Safety Information on page 11, and the accompanying Full Prescribing Information in pocket.

RAVICTI® (glycerol phenylbutyrate) Oral Liquid
Rethink potential.

How to adjust the RAVICTI (glycerol phenylbutyrate) Oral Liquid dosage for targeted ammonia control

Steps to help ensure patients are receiving the ammonia control they need[3,4]

Assess plasma ammonia → **Consider PBA metabolite biomarkers** → **Order PBA metabolite test and make it part of routine analysis**

Assess plasma ammonia

- When plasma ammonia is elevated, increase the RAVICTI dosage in patients 6 years of age and older to reduce the fasting ammonia level to **less than half the upper limit of normal (ULN)**.[1]
- In infants and young children (generally below 6 years of age) in whom obtaining fasting ammonia is problematic due to frequent feedings, it is recommended that the first ammonia of the morning be kept below the ULN.[1,a]
- Closely monitor ammonia levels of 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.[1]

[a]Instruct patients to abstain from eating or drinking any foods or liquids 4 to 6 hours before plasma ammonia levels are to be measured.[5]

SELECT IMPORTANT SAFETY INFORMATION—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.

Please review the RAVICTI Important Safety Information on page 10 and the BUPHENYL (sodium phenylbutyrate) Important Safety Information on page 11, and the accompanying Full Prescribing Information in pocket.

Use PBA metabolite biomarkers to help guide RAVICTI dosing decisions[1,3,4]

TEST	KNOW	APPLY
Plasma PAA	• PAA is the major metabolite of RAVICTI.[1] • Elevated levels of PAA (>500 µg/mL) are associated with neurotoxicity.[1]	• Reduce the RAVICTI dosage if symptoms of vomiting, nausea, headache, somnolence, or confusion are present in the absence of high ammonia or intercurrent illness.[1]
Plasma PAA:PAGN	• Due to its relative stability over a 24-hour period, the PAA:PAGN ratio may better predict peak PAA levels through a single blood draw.[3]	• High PAA:PAGN ratios may be correlated with neurotoxic PAA levels.[1,3] • Low PAA:PAGN ratios (<1) have been observed in patients without significant PAA accumulation.[1]
Urinary PAGN	• Approximately 70% of an administered PBA dose will be converted to urinary PAGN.[1,b]	• Urinary PAGN is an indicator of the effectiveness of PBA-based therapies and may be used to assess patient compliance issues.[4]

[b]If urinary 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.[1]

It's easy to get your patients tested:

Horizon is dedicated to the well-being of all patients with UCDs. Phenylbutyrate metabolite analysis testing is available through Baylor Genetics and sponsored by Horizon. Test kits can be ordered **at no charge to you or your patients**.

1. Order phenylbutyrate metabolite analysis kits online at **http://bmgl.com/testing/order-kits**.
2. Send the patient specimens to Baylor Genetics.
3. Receive a comprehensive report of test results.

SELECT IMPORTANT SAFETY INFORMATION—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.

Please review the RAVICTI Important Safety Information on page 10 and the BUPHENYL (sodium phenylbutyrate) Important Safety Information on page 11, and the accompanying Full Prescribing Information in pocket.

RAVICTI®
(glycerol phenylbutyrate) Oral Liquid
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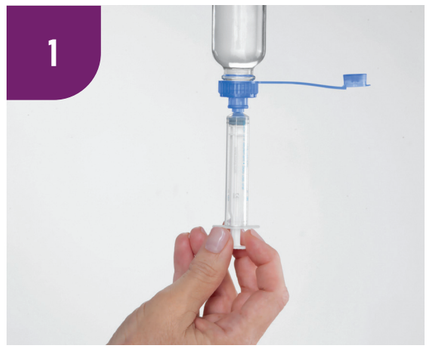
Steps for nasogastric or gastrostomy tube (g-tube)

Oral administration is recommended for patients who can swallow, even for those with nasogastric and/or g-tubes. However, for patients who cannot swallow, a nasogastric tube or g-tube may be used to administer RAVICTI (glycerol phenylbutyrate) Oral Liquid as follows[1]:



1. Use an oral syringe to withdraw the prescribed dose of RAVICTI from the bottle.

2. Place the tip of the syringe into the tip of the nasogastric tube or g-tube.

3. Using the plunger of the syringe, administer RAVICTI into the tube.

4. Using a large-capacity syringe, **flush once** with 10 mL of water or formula and allow the flush to drain.
5. **If necessary, flush a second time** with an additional 10 mL of water or formula to clear the tube.

SELECT IMPORTANT SAFETY INFORMATION—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.

Please review the RAVICTI Important Safety Information on page 10 and the BUPHENYL (sodium phenylbutyrate) Important Safety Information on page 11, and the accompanying Full Prescribing Information in pocket.

Important information

- RAVICTI should be stored between 68°F and 77°F (20°C and 25°C) and taken with meals.[1]
- Because RAVICTI is a liquid that is glycerol based, flushing the nasogastric or g-tube is required to ensure that the complete dose is administered.[1]
- For patients who require a volume of less than 1 mL per dose via nasogastric or g-tube, the delivered dose may be less than anticipated; closely monitor the ammonia levels of these patients.[1]

SELECT IMPORTANT SAFETY INFORMATION—DRUG INTERACTIONS

- 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.

Please review the RAVICTI Important Safety Information on page 10 and the BUPHENYL (sodium phenylbutyrate) Important Safety Information on page 11, and the accompanying Full Prescribing Information in pocket.

RAVICTI®
(glycerol phenylbutyrate) Oral Liquid
Rethink potential.

INDICATION and IMPORTANT SAFETY INFORMATION FOR RAVICTI® (glycerol phenylbutyrate) ORAL LIQUID

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

- *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. 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.

Please see accompanying Full Prescribing Information in pocket.

INDICATION and IMPORTANT SAFETY INFORMATION for BUPHENYL® (sodium phenylbutyrate) Tablets and Powder

INDICATION

BUPHENYL (sodium phenylbutyrate) Tablets for oral administration and BUPHENYL (sodium phenylbutyrate) Powder for oral, nasogastric, or gastrostomy tube administration are indicated as adjunctive therapy in the chronic management of patients with urea cycle disorders (UCDs) involving deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid synthetase (AS).

BUPHENYL is indicated in all patients with neonatal-onset deficiency (complete enzymatic deficiency, presenting within the first 28 days of life). It is also indicated in patients with late-onset disease (partial enzymatic deficiency, presenting after the first month of life) who have a history of hyperammonemic encephalopathy.

BUPHENYL must be used with dietary protein restriction and, in some cases, essential amino acid supplementation.

Any episode of acute hyperammonemia should be treated as a life-threatening emergency.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- *Acute hyperammonemia*: BUPHENYL should not be used to manage acute hyperammonemia, which is a medical emergency.

WARNINGS AND PRECAUTIONS

BUPHENYL should not be administered to patients with known hypersensitivity to sodium phenylbutyrate or any component of this preparation.

- Use caution with administering BUPHENYL to patients with:
  - Congestive heart failure or severe renal insufficiency, and in clinical states in which there is sodium retention with edema.
  - Hepatic or renal insufficiency or inborn errors of beta oxidation.
- Probenecid may affect renal excretion of the conjugated product of BUPHENYL as well as its metabolite.
- Use of corticosteroids may cause the breakdown of body protein and increase plasma ammonia levels.
- There have been published reports of hyperammonemia being induced by haloperidol and by valproic acid.

ADVERSE REACTIONS

- The most common adverse reactions (≥3%) reported in BUPHENYL clinical trials were decreased appetite, body odor, bad taste or taste aversion.
- In female patients, amenorrhea/menstrual dysfunction (irregular menstrual cycles) occurred in 23% of the menstruating patients.
- Neurotoxicity was reported in cancer patients receiving intravenous phenylacetate. Manifestations were predominately somnolence, fatigue, and lightheadedness; with less frequent headache, dysgeusia, hypoacusis, disorientation, impaired memory, and exacerbation of a pre-existing neuropathy.
- Laboratory adverse events occurring in >2% of UCD patients by body system were:
  - *Metabolic:* acidosis, alkalosis, hyperchloremia, and hypophosphatemia
  - *Nutritional:* hypoalbuminemia and decreased total protein
  - *Hepatic:* increased alkaline phosphatase and increased liver transaminases
  - *Hematologic:* anemia, leukopenia, leukocytosis, and thrombocytopenia

USE IN SPECIFIC POPULATIONS

Pregnancy: BUPHENYL should be used with caution in patients who are pregnant or planning to become pregnant. Animal reproduction studies have not been conducted with BUPHENYL. It is not known whether BUPHENYL can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

Lactation: breastfeeding is not recommended during treatment with BUPHENYL. There are no data on the presence of BUPHENYL in human milk.

Please see accompanying Full Prescribing Information in pocket.

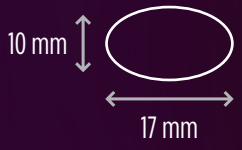
RAVICTI (glycerol phenylbutyrate) Oral Liquid: Effective ammonia control that fits into your patients' lives[1]

Nearly tasteless and odorless[2]

No pill or powder preparation[1]

Taken with meals via oral dosing syringe[1]

- RAVICTI is the only U.S. Food and Drug Administration–approved oral liquid for the treatment of patients with UCDs.[1]
- Administer RAVICTI orally with food or formula; for infants who are breastfed, administer just prior to breastfeeding.[1]
- RAVICTI can be taken orally even in patients with a nasogastric tube or g-tube.[1]
- For patients who require a volume of less than 1 mL per dose via nasogastric or g-tube, the delivered dose may be less than anticipated; closely monitor the ammonia levels of these patients.[1]
- The maximum daily dosage of RAVICTI (17.5 mL) is equivalent to 40 tablets of sodium phenylbutyrate.[1,2]



BUPHENYL® (sodium phenylbutyrate) 500-mg tablet; actual size[6]

Please review the RAVICTI Important Safety Information on page 10 and the BUPHENYL (sodium phenylbutyrate) Important Safety Information on page 11, and the accompanying Full Prescribing Information in pocket.

References: 1. RAVICTI (glycerol phenylbutyrate) Oral Liquid [prescribing information] Horizon. **2.** Diaz GA, Krivitzky LS, Mokhtarani M, et al. Ammonia control and neurocognitive outcome among urea cycle disorder patients treated with glycerol phenylbutyrate. *Hepatology.* 2013;57(6):2171-2179. doi:10.1002/hep.26058. **3.** 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. **4.** 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. **5.** Häberle J. Clinical practice: the management of hyperammonemia. *Eur J Pediatr.* 2011;170(1):21-34. doi:10.1007/s00431-010-1369-2. **6.** Findmyfills.org. Pictures for white elliptical/oval pill imprint UCY 500. http://www.findmyfills.org/qas/pictures-for-white-elliptical-oval-pill-imprint-ucy-500/. Accessed March 28, 2017.

HORIZON

RAVICTI®
(glycerol phenylbutyrate) Oral Liquid
Rethink potential.

SELECTED AGE RANGE: Birth to less than 2 years of age

See reverse side for patients 2 years of age and older.

FROM TABLETS

Total daily dosage of sodium phenylbutyrate tablets (g)[1]	Equals **total daily dosage** of RAVICTI (glycerol phenylbutyrate) Oral Liquid (mL)[1]	Each dose of RAVICTI is rounded up to the nearest 0.1 mL (to be given TID)[1,a]
2	1.72	0.6
3	2.58	0.9
4	3.44	1.2
5	4.30	1.5
6	5.16	1.8
7	6.02	2.1
8	6.88	2.3
9	7.74	2.6
10	8.60	2.9
11	9.46	3.2
12	10.32	3.5
13	11.18	3.8
14	12.04	4.1
15	12.90	4.3
16	13.76	4.6
17	14.62	4.9
18	15.48	5.2
19	16.34	5.5
20	17.20	5.8

FROM POWDER

Total daily dosage of sodium phenylbutyrate powder (g)[1]	Equals **total daily dosage** of RAVICTI (glycerol phenylbutyrate) Oral Liquid (mL)[1]	Each dose of RAVICTI is rounded up to the nearest 0.1 mL (to be given TID[1,a]
2	1.62	0.6
3	2.43	0.9
4	3.24	1.1
5	4.05	1.4
6	4.86	1.7
7	5.67	1.9
8	6.48	2.2
9	7.29	2.5
10	8.10	2.7
11	8.91	3.0
12	9.72	3.3
13	10.53	3.6
14	11.34	3.8
15	12.15	4.1
16	12.96	4.4
17	13.77	4.6
18	14.58	4.9
19	15.39	5.2
20	16.20	5.4

[a]For patients less than 2 years of age, administer RAVICTI in 3 or more equally divided doses, each rounded up to the nearest 0.1 mL; if administering more than 3 doses, adjust the amount of each dose accordingly.

SELECTED AGE RANGE: 2 years of age and older
See reverse side for patients less than 2 years of age.

FROM TABLETS

Total daily dosage of sodium phenylbutyrate tablets (g)[1]	Equals **total daily dosage** of RAVICTI (glycerol phenylbutyrate) Oral Liquid (mL)[1]	Each dose of RAVICTI is rounded up to the nearest 0.5 mL (to be given TID)[1,a]
2	1.72	1.0
3	2.58	1.0
4	3.44	1.5
5	4.30	1.5
6	5.16	2.0
7	6.02	2.5
8	6.88	2.5
9	7.74	3.0
10	8.60	3.0
11	9.46	3.5
12	10.32	3.5
13	11.18	4.0
14	12.04	4.5
15	12.90	4.5
16	13.76	5.0
17	14.62	5.0
18	15.48	5.5
19	16.34	5.5
20	17.20	5.8[a]

FROM POWDER

Total daily dosage of sodium phenylbutyrate powder (g)[1]	Equals **total daily dosage** of RAVICTI (glycerol phenylbutyrate) Oral Liquid (mL)[1]	Each dose of RAVICTI is rounded up to the nearest 0.5 mL (to be given TID)[1]
2	1.62	1.0
3	2.43	1.0
4	3.24	1.5
5	4.05	1.5
6	4.86	2.0
7	5.67	2.0
8	6.48	2.5
9	7.29	2.5
10	8.10	3.0
11	8.91	3.0
12	9.72	3.5
13	10.53	4.0
14	11.34	4.0
15	12.15	4.5
16	12.96	4.5
17	13.77	5.0
18	14.58	5.0
19	15.39	5.5
20	16.20	5.5

[a]When converting 20 g of sodium phenylbutyrate tablets to RAVICTI for patients 2 years of age and older, the rounding of doses has been adjusted so that the total daily dosage does not exceed the maximum.[1]