Brand Name	Ravicti
Active Ingredient(s)	glycerol phenylbutyrate
Strength	1.1 g/mL
Dosage Form	oral liquid
Inactive Ingredients	(none)
NDC	75987-050-06, 75987-050-07
DIN	02453304
Canadian Distributor	Horizon Therapeutics Ireland DAC 70 St. Stephen's Green Saint Kevin's, Dublin 2. D02E2X4 Ireland
NDA Number	NDA203284
US Distributor (NDA Holder)	Horizon Therapeutics USA, Inc. 150 Saunders Road; Lake Forest, Illinois 60045 USA
Manufacturer (Final Packager)	Not available
API Manufacturer	Not available
Relationship to Sponsor	The Sponsor may have or have had agreements with the U.S. manufacturer for rebates. The Sponsor has no relationship with the foreign manufacturer.

Current FDA-approved Package Insert

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

Dosage and Administration (2.1, 2.6) 9/2021

INDICATIONS AND USAGE

RAVICTI is a nitrogen-binding agent indicated 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. (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, 8.7)

DOSAGE FORMS AND STRENGTHS

Oral liquid: 1.1 g/mL. (3)

CONTRAINDICATIONS

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)
- 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 at 1-866-479-6742 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: 9/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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 (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.
- Instruct patients to use the RAVICTI bottle and oral syringe as follows:
  - Use a new reclosable bottle cap adapter with each new bottle that is opened.
  - Open the RAVICTI bottle and twist on the new reclosable bottle cap adapter.
  - Use a new and dry oral syringe to withdraw each prescribed dose of RAVICTI.
  - Discard the oral syringe after each dose.
  - Tightly close the tethered tab on the reclosable bottle cap adapter after each use.
  - Do not rinse the reclosable bottle cap adapter.
  - Discard bottle and any remaining contents 28 days after opening.
  - If water or moisture enters the RAVICTI bottle, the contents will become cloudy in appearance. If the contents of the bottle appear cloudy at any time, do not use the remaining RAVICTI in the bottle and return it to the pharmacy to be discarded.
- Instruct that RAVICTI should be administered just prior to breastfeeding in infants who are breastfeeding.
- 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 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 plasma ammonia levels during treatment with RAVICTI and when changing the dosage of RAVICTI.

The methods used for measuring plasma ammonia levels vary among individual laboratories and values obtained using different assay methods may not be interchangeable. Normal ranges and therapeutic target levels for plasma ammonia depend upon the assay method used

by the individual laboratory. During treatment with RAVICTI, refer to the assay-specific normal ranges and to the therapeutic target ranges for plasma ammonia.

Normal Plasma Ammonia

In patients treated with RAVICTI who experience neurologic symptoms (e.g. nausea, vomiting, headache, somnolence or confusion) in the absence of high plasma ammonia or other intercurrent illness to explain these symptoms, consider reducing the RAVICTI dosage and clinically monitor patients for potential neurotoxicity from high phenylacetate (PAA) concentrations. If available, obtain measurements of plasma PAA concentrations and plasma phenylacetylglutamine (PAGN) to calculate the ratio of plasma PAA to PAGN which may help to guide RAVICTI dosing. The PAA to PAGN ratio has generally been less than 1 in patients with UCDs who did not have significant plasma PAA accumulation. In general, a high PAA to PAGN ratio may indicate a slower or less efficient conjugation reaction to form PAGN, which may lead to increases in PAA without further conversion to PAGN *[see Warnings and Precautions (5.1), Clinical Pharmacology (12.3)]*.

Elevated Plasma Ammonia

In patients 6 years and older, when plasma ammonia is elevated, increase the RAVICTI dosage to maintain fasting plasma ammonia to less than half the upper limit of normal (ULN). 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. If available, the ratio of PAA to PAGN in the same plasma sample may provide additional information to assist in dosage adjustment decisions *[see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]*.

Dietary Protein Intake

If available, urinary phenylacetylglutamine (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 insufficient to cover daily dietary protein intake and the fasting ammonia is greater than half the ULN, the RAVICTI dosage should be increased. The amount of dosage adjustment should factor in the amount of dietary protein that has not been covered, as indicated by the 24-hour U-PAGN output, 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)]*.

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 recommended dosing range (4.5 mL/m^2/day) and the dosage should be kept at the lowest necessary to control the patient's plasma ammonia *[see Use in Specific Populations (8.7)]*.

2.6 Preparation for Nasogastric Tube or Gastrostomy Tube Administration

It is recommended that all patients who can swallow take RAVICTI orally, even those with nasogastric and/or gastrostomy tubes. For patients who cannot swallow, a nasogastric tube or gastrostomy tube may be used to administer RAVICTI as follows:

- Utilize a new dry oral syringe to withdraw each prescribed dosage of RAVICTI from the bottle.
- Place the tip of the syringe into the nasogastric/gastrostomy tube.
- Utilizing the plunger of the syringe, administer RAVICTI into the tube.
- Use a separate syringe to flush the nasogastric/gastrostomy tube. Flush once with 10 mL of water or formula and allow the flush to drain.
- If needed, flush a second time with an additional 10 mL of water or formula to clear the tube.

For 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. Therefore, these patients should be closely monitored using ammonia levels following initiation of RAVICTI dosing or dosage adjustments.

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 with known hypersensitivity to phenylbutyrate. Signs of hypersensitivity include wheezing, dyspnea, coughing, hypotension, flushing, nausea, and rash.

5 WARNINGS AND PRECAUTIONS

5.1 Neurotoxicity

Increased exposure to PAA, the major metabolite of RAVICTI, may be associated with neurotoxicity in patients with UCDs. In a study of adult cancer patients, subjects received sodium phenylacetate administered as a 1-hour infusion twice daily at two dose levels of 125 and 150 mg/kg for a 2-week period. Of 18 subjects enrolled, 7 had a history of primary central nervous system tumor. Signs and symptoms of potential PAA neurotoxicity, which were reversible, were reported at plasma PAA concentrations above 500 micrograms/mL and included somnolence, fatigue, lightheadedness, headache, dysgeusia, hypoacusis,

disorientation, impaired memory, and exacerbation of preexisting neuropathy. PAA concentrations were not measured when symptoms resolved.

In healthy subjects, after administration of 4 mL and 6 mL RAVICTI 3 times daily (13.2 g/day and 19.8 g/day, respectively) for 3 days, a dose-dependent increase in non-serious nervous system adverse reactions were observed. In subjects who had nervous system adverse reactions, plasma PAA concentrations, which were measured on Day 3 per protocol and not always at onset of symptoms, ranged from 8 to 56 micrograms/mL with 4 mL RAVICTI 3 times daily and from 31 to 242 micrograms/mL with 6 mL RAVICTI 3 times daily.

In clinical trials in patients with UCDs who had been on sodium phenylbutyrate prior to administration of RAVICTI, adverse reactions of headache, fatigue, symptoms of peripheral neuropathy, seizures, tremor and/or dizziness were reported. No correlation between plasma PAA concentration and neurologic symptoms was identified but plasma PAA concentrations were generally not consistently measured at the time of neurologic symptom occurrence *[see Clinical Pharmacology (12.3)]*.

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 *[see Dosage and Administration (2.4)]*.

5.2 Pancreatic Insufficiency or Intestinal Malabsorption

Exocrine pancreatic enzymes hydrolyze RAVICTI in the small intestine, separating the active moiety, phenylbutyrate, from glycerol. This process allows phenylbutyrate to be absorbed into the circulation. 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 in patients with pancreatic insufficiency or intestinal malabsorption.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Neurotoxicity *[see Warnings and Precautions (5.1)]*
- Pancreatic insufficiency or Intestinal Malabsorption *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Assessment of adverse reactions was based on exposure of 45 adult patients (31 female and 14 male) with UCD subtype deficiencies of ornithine transcarbamylase (OTC, n=40), carbamoyl phosphate synthetase (CPS, n=2), and argininosuccinate synthetase (ASS, n=1) in

a randomized, double-blind, active-controlled (RAVICTI vs sodium phenylbutyrate), crossover, 4-week study (Study 1) that enrolled patients 18 years of age and older *[see Clinical Studies (14.1)]*. One of the 45 patients received only sodium phenylbutyrate prior to withdrawing on day 1 of the study due to an adverse reaction.

The most common adverse reactions (occurring in at least 10% of patients) reported during short-term treatment with RAVICTI were diarrhea, flatulence, and headache. Table 1 summarizes adverse reactions occurring in 2 or more patients treated with RAVICTI or sodium phenylbutyrate (incidence of at least 4% in either treatment arm).

Table 1: Adverse Reactions Reported in 2 or More Adult Patients with UCDs (at least 4% in Either Treatment Arm) in Study 1

	Number (%) of Patients in Study 1	
	Sodium Phenylbutyrate (N = 45)	**RAVICTI (N = 44)**
Diarrhea	3 (7)	7 (16)
Headache	4 (9)	6 (14)
Flatulence	1 (2)	6 (14)
Abdominal pain	2 (4)	3 (7)
Vomiting	2 (4)	3 (7)
Decreased appetite	2 (4)	3 (7)
Fatigue	1 (2)	3 (7)
Dyspepsia	3 (7)	2 (5)
Nausea	3 (7)	1 (2)
Dizziness	4 (9)	0
Abdominal discomfort	3 (7)	0

Other Adverse Reactions

RAVICTI has been evaluated in 77 patients with UCDs (51 adult and 26 pediatric patients ages 2 years to 17 years) in 2 open-label long-term studies, in which 69 patients completed 12 months of treatment with RAVICTI (median exposure = 51 weeks). During these studies there were no deaths.

Adverse reactions reported in at least 10% of adult patients were nausea, vomiting, diarrhea, decreased appetite, dizziness, headache, and fatigue.

Adverse reactions reported in at least 10% of pediatric patients ages 2 years to 17 years were upper abdominal pain, rash, nausea, vomiting, diarrhea, decreased appetite, and headache.

RAVICTI has been evaluated in 17 patients with UCDs ages 2 months to less than 2 years in 3 open-label studies. The median exposure was 6 months (range 0.2 to 20 months). Adverse reactions reported in at least 10% of pediatric patients aged 2 months to less than 2 years were neutropenia, vomiting, constipation, diarrhea, pyrexia, hypophagia, cough, nasal congestion, rhinorrhea, rash, and papule.

RAVICTI has been evaluated in 16 patients with UCDs less than 2 months of age (age range 0.1 to 2 months, median age 0.5 months) in a single, open-label study. The median exposure was 10 months (range 2 to 20 months). Adverse reactions reported in at least 10% of pediatric patients aged less than 2 months were 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.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of RAVICTI. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

- Abnormal body odor, including from skin, hair and urine
- Retching and gagging
- Dysgeusia or burning sensation in mouth

7 DRUG INTERACTIONS

7.1 Potential for Other Drugs to Affect Ammonia

Corticosteroids

Use of corticosteroids may cause the breakdown of body protein and increase plasma ammonia levels. Monitor ammonia levels closely when corticosteroids and RAVICTI are used concomitantly.

Valproic Acid and Haloperidol

Hyperammonemia may be induced by haloperidol and by valproic acid. Monitor ammonia levels closely when use of valproic acid or haloperidol is necessary in patients with UCDs.

7.2 Potential for Other Drugs to Affect RAVICTI

Probenecid

Probenecid may inhibit the renal excretion of metabolites of RAVICTI including PAGN and PAA.

7.3 Potential for RAVICTI to Affect Other Drugs

Drugs with narrow therapeutic index that are substrates of CYP3A4

RAVICTI is a weak inducer of CYP3A4 in humans. Concomitant use of RAVICTI may decrease the systemic exposure to drugs that are substrates of CYP3A4. Monitor for decreased efficacy of drugs with narrow therapeutic index (e.g., alfentanil, quinidine, cyclosporine) *[see Clinical Pharmacology (12.3)]*.

Midazolam

Concomitant use of RAVICTI decreased the systemic exposure of midazolam. Monitor for suboptimal effect of midazolam in patients who are being treated with RAVICTI.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited available data with RAVICTI use in pregnant women are insufficient to inform a drug-associated risk of major birth defects and miscarriage. In an animal reproduction study, administration of oral glycerol phenylbutyrate to pregnant rabbits during organogenesis at doses up to 2.7–times the dose of 6.87 mL/m^2/day in adult patients resulted in maternal toxicity, but had no effects on embryo-fetal development. In addition, there were no adverse developmental effects with administration of oral glycerol phenylbutyrate to pregnant rats during organogenesis at 1.9 times the dose of 6.87 mL/m^2/day in adult patients; however, maternal toxicity, reduced fetal weights, and variations in skeletal development were observed in pregnant rats administered oral glycerol phenylbutyrate during organogenesis at doses greater than or equal to 5.7 times the dose of 6.87 mL/m^2/day in adult patients *[*see *Data]*. Report pregnancies to Horizon at 1-866-479-6742.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

Oral administration of glycerol phenylbutyrate during the period of organogenesis up to 350 mg/kg/day in rabbits produced maternal toxicity, but no effects on embryo-fetal development. The dose of 350 mg/kg/day in rabbits is approximately 2.7 times the dose of 6.87 mL/m^2/day in adult patients, based on combined area under the plasma concentration-time curve [AUCs] for PBA and PAA. In rats, at an oral dose of 300 mg/kg/day of glycerol phenylbutyrate (1.9 times the dose of 6.87 mL/m^2/day in adult patients, based on combined AUCs for PBA and PAA) during the period of organogenesis, no effects on embryo-fetal development were observed. Doses of 650 mg/kg/day or greater produced maternal toxicity and adverse effects on embryo-fetal development including reduced fetal weights and cervical ribs at the 7th cervical vertebra. The dose of 650 mg/kg/day in rats is approximately 5.7 times the dose of 6.87 mL/m^2/day in adult patients, based on combined AUCs for PBA and PAA. No developmental abnormalities, effects on growth, or effects on learning and memory were observed through maturation of offspring following oral administration in pregnant rats with up to 900 mg/kg/day of glycerol phenylbutyrate (8.5 times the dose of 6.87 mL/m^2/day in adult patients, based on combined AUCs for PBA and PAA) during organogenesis and lactation.

8.2 Lactation

Risk Summary

There are no data on the presence of RAVICTI in human milk, the effects on the breastfed infant, or the effects on milk production. Because of the potential for serious adverse reactions, including neurotoxicity and tumorigenicity in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with RAVICTI.

8.4 Pediatric Use

Patients 2 Years to 17 Years of Age

The safety and effectiveness of RAVICTI in patients 2 years to less than 18 years of age have been established in 3 clinical studies: 2 open-label, fixed-sequence, switchover clinical studies from sodium phenylbutyrate to RAVICTI, and 1 long-term, open label safety study *[see Adverse Reactions (6.1), Clinical Studies (14.2)]*.

Patients Less Than 2 Years of Age

The safety and effectiveness of RAVICTI in patients with UCDs less than 2 years of age have been established in 3 open-label studies. Pharmacokinetics and pharmacodynamics (plasma ammonia), and safety were studied in 17 patients aged 2 months to less than 2 years of age and in 16 patients less than 2 months of age *[see Adverse Reactions (6.1), Clinical Studies (14.3)]*.

Juvenile Animal Toxicity Data

In a juvenile rat study with daily oral dosing performed on postpartum day 2 through mating and pregnancy after maturation, terminal body weight was dose-dependently reduced by up to 16% in males and 12% in females at 900 mg/kg/day or higher (3 times the dose of 6.87 mL/m^2/day in adult patients, based on combined AUCs for PBA and PAA). Learning, memory, and motor activity endpoints were not affected. However, fertility (number of pregnant rats) was decreased by up to 25% at 650 mg/kg/day or higher (2.6 times the dose of 6.87 mL/m^2/day in adult patients, based on combined AUCs for PBA and PAA).

8.5 Geriatric Use

Clinical studies of RAVICTI did not include sufficient numbers of subjects 65 years of age and older to determine whether they respond differently than younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Renal Impairment

The efficacy and safety of RAVICTI in patients with renal impairment are unknown. Monitor ammonia levels closely when starting patients with impaired renal function on RAVICTI.

8.7 Hepatic Impairment

No studies were conducted in patients with UCDs and hepatic impairment. Because conversion of PAA to PAGN occurs in the liver, patients with hepatic impairment may have

reduced conversion capability and higher plasma PAA and PAA to PAGN ratio *[see Clinical Pharmacology (12.3)]*. Therefore, dosage for patients with moderate to severe hepatic impairment should be started at the lower end of the recommended dosing range and should be kept on the lowest dose necessary to control their ammonia levels *[see Dosage and Administration (2.5)]*.

10 OVERDOSAGE

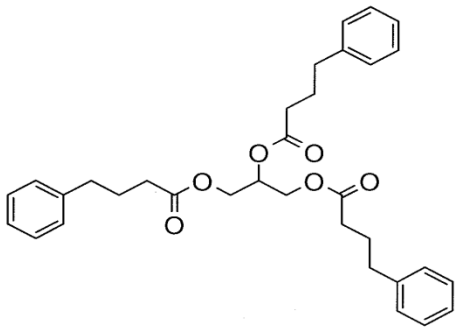
While there is no experience with overdosage in human clinical trials, PAA, a toxic metabolite of RAVICTI, can accumulate in patients who receive an overdose *[see Warnings and Precautions (5.1)]*.

If over-exposure occurs, call your Poison Control Center at 1-800-222-1222 for current information on the management of poisoning or overdosage.

11 DESCRIPTION

RAVICTI (glycerol phenylbutyrate) is a clear, colorless to pale yellow oral liquid. It is insoluble in water and most organic solvents, and it is soluble in dimethylsulfoxide (DMSO) and greater than 65% acetonitrile.

Glycerol phenylbutyrate is a nitrogen-binding agent. It is a triglyceride containing 3 molecules of PBA linked to a glycerol backbone, the chemical name of which is benzenebutanoic acid, 1', 1' ' –(1,2,3-propanetriyl) ester with a molecular weight of 530.67. It has a molecular formula of $C_{33}H_{38}O_6$. The structural formula is:



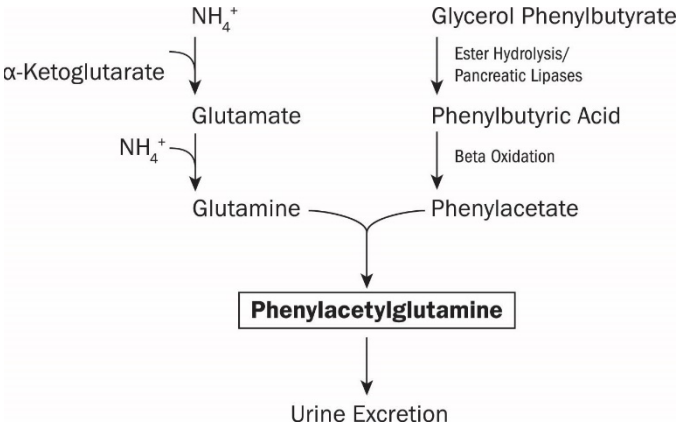
12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

UCDs are inherited deficiencies of enzymes or transporters necessary for the synthesis of urea from ammonia (NH_3, NH_4^+). Absence of these enzymes or transporters results in the accumulation of toxic levels of ammonia in the blood and brain of affected patients. RAVICTI is a triglyceride containing 3 molecules of PBA. PAA, the major metabolite of PBA, is the active moiety of RAVICTI. PAA conjugates with glutamine (which contains 2 molecules of nitrogen) via acetylation in the liver and kidneys to form PAGN, which is

excreted by the kidneys (Figure 1). On a molar basis, PAGN, like urea, contains 2 moles of nitrogen and provides an alternate vehicle for waste nitrogen excretion.

Figure 1: RAVICTI Mechanism of Action



12.2 Pharmacodynamics

Pharmacological Effects

In clinical studies, total 24-hour area under the plasma concentration-time curve (AUC) of ammonia levels was comparable at steady state during the switchover period between RAVICTI and sodium phenylbutyrate *[see Clinical Studies (14)]*.

Cardiac Electrophysiology

The effect of multiple doses of RAVICTI 13.2 g/day and 19.8 g/day (approximately 69% and 104% of the maximum recommended daily dosage) on QTc interval was evaluated in a randomized, placebo- and active-controlled (moxifloxacin 400 mg), four-treatment-arm, crossover study in 57 healthy subjects. The upper bound of the one-sided 95% CI for the largest placebo-adjusted, baseline-corrected QTc, based on individual correction method (QTcI) for RAVICTI, was below 10 ms.

12.3 Pharmacokinetics

Absorption

RAVICTI is a pro-drug of PBA. Upon oral ingestion, PBA is released from the glycerol backbone in the gastrointestinal tract by lipases. PBA derived from RAVICTI is further converted by β-oxidation to PAA.

In healthy, fasting adult subjects receiving a single oral dose of 2.9 mL/m^2 of RAVICTI, peak plasma levels of PBA, PAA, and PAGN occurred at 2 hours, 4 hours, and 4 hours, respectively. Upon single-dose administration of RAVICTI, plasma concentrations of PBA were quantifiable in 15 of 22 participants at the first sample time postdose (0.25 hours).

Mean maximum concentration (C_{max}) for PBA, PAA, and PAGN was 37.0 micrograms/mL, 14.9 micrograms/mL, and 30.2 micrograms/mL, respectively. In healthy subjects, intact glycerol phenylbutyrate was detected in plasma. While the study was inconclusive, the incomplete hydrolysis of glycerol phenylbutyrate cannot be ruled out.

In healthy subjects, the systemic exposure to PAA, PBA, and PAGN increased in a dose-dependent manner. Following 4 mL of RAVICTI 3 times a day for 3 days, the mean C_{max} and AUC were 66 micrograms/mL and 930 micrograms•h/mL for PBA and 28 micrograms/mL and 942 micrograms•h/mL for PAA, respectively. In the same study, following 6 mL of RAVICTI three times a day for 3 days, mean C_{max} and AUC were 100 micrograms/mL and 1400 micrograms•h/mL for PBA and 65 µg/mL and 2064 micrograms•h/mL for PAA, respectively.

In adult patients with UCDs receiving multiple doses of RAVICTI, maximum plasma concentrations at steady state ($C_{max,ss}$) of PBA, PAA, and PAGN occurred at 8 hours, 12 hours, and 10 hours, respectively, after the first dose in the day. Intact glycerol phenylbutyrate was not detectable in plasma in patients with UCDs.

In clinical studies of RAVICTI in patients with UCDs, the peak observed PAA concentrations by age group are shown in Table 2.

Table 2: Peak PAA Concentrations in Patients with UCDs Treated with RAVICTI in Clinical Trials

Age Range	RAVICTI Dose	Mean Peak PAA Concentration* (SD)	Median Peak PAA Concentration * (Range)
Less than 2 months (n=16)	3.1 to 12.7 mL/m^2/day (3.4 to 14 g/m^2/day)	257 (162)	205 (96 to 707)
2 months to less than 2 years (n=17)	3.3 to 12.3 mL/m^2/day (3.7 to 13.5 g/m^2/day)	142 (299)	35 (1 to 1215)
2 years to 17 years (n=53)	1.4 to 13.7 mL/m^2/day (1.5 to 15.1 g/m^2/day)	70 (79)	50 (1 to 410)
Adults (n=43)	0.6 to 14 mL/m^2/day (0.7 to 15.4 g/m^2/day)	39 (40)	25 (1.6 to 178)

*micrograms/mL

Distribution

In vitro, the extent of plasma protein binding for ^{14}C-labeled metabolites was 81% to 98% for PBA (over 1 to 250 micrograms/mL), and 37% to 66% for PAA (over 5 to 500 micrograms/mL). The protein binding for PAGN was 7% to 12% and no concentration effects were noted.

Elimination

Metabolism

Upon oral administration, pancreatic lipases hydrolyze RAVICTI (i.e., glycerol phenylbutyrate), and release PBA. PBA undergoes β-oxidation to PAA, which is conjugated

with glutamine in the liver and in the kidney through the enzyme phenylacetyl-CoA: L-glutamine-N-acetyltransferase to form PAGN. PAGN is subsequently eliminated in the urine.

Saturation of conjugation of PAA and glutamine to form PAGN was suggested by increases in the ratio of plasma PAA to PAGN with increasing dose and with increasing severity of hepatic impairment.

In healthy subjects, after administration of 4 mL, 6 mL, and 9 mL 3 times daily for 3 days, the ratio of mean $AUC_{0\text{-}23h}$ of PAA to PAGN was 1, 1.25, and 1.6, respectively. In a separate study, in patients with hepatic impairment (Child-Pugh B and C), the ratios of mean C_{max} values for PAA to PAGN among all patients dosed with 6 mL and 9 mL twice daily were 3 and 3.7.

In *in vitro* studies, the specific activity of lipases for glycerol phenylbutyrate was in the following decreasing order: pancreatic triglyceride lipase, carboxyl ester lipase, and pancreatic lipase–related protein 2. Further, glycerol phenylbutyrate was hydrolyzed *in vitro* by esterases in human plasma. In these *in vitro* studies, a complete disappearance of glycerol phenylbutyrate did not produce molar equivalent PBA, suggesting the formation of mono- or bis-ester metabolites. However, the formation of mono- or bis-esters was not studied in humans.

Excretion

The mean (SD) percentage of administered PBA excreted as PAGN was approximately 69% (17) in adults and 66% (24) in pediatric patients with UCDs at steady state. PAA and PBA represented minor urinary metabolites, each accounting for less than 1% of the administered dose of PBA.

Specific Populations

Age: Pediatric Population

Population pharmacokinetic modeling and dosing simulations suggest body surface area to be the most significant covariate explaining the variability of PAA clearance. PAA clearance was 10.9 L/h, 16.4 L/h, and 24.4 L/h, respectively, for patients ages 3 to 5, 6 to 11, and 12 to 17 years with UCDs.

In pediatric patients with UCDs (n = 14) ages 2 months to less than 2 years, PAA clearance was 6.8 L/h.

In pediatric patients with UCDs (n = 16) ages less than 2 months, PAA clearance was 3.8 L/h. The mean peak ratio of PAA to PAGN in UCD patients aged birth to less than 2 months was higher (mean: 1.6; range 0.1 to 7.1) than that of UCD patients aged 2 months to less than 2 years (mean 0.5; range 0.1 to 1.2).

Sex

In healthy adult subjects, a gender effect was found for all metabolites, with women generally having higher plasma concentrations of all metabolites than men at a given dose level. In healthy female subjects, mean C_{max} for PAA was 51 and 120% higher than in male volunteers after administration of 4 mL and 6 mL 3 times daily for 3 days, respectively. The dose normalized mean $AUC_{0\text{-}23h}$ for PAA was 108% higher in females than in males.

Renal Impairment

The pharmacokinetics of RAVICTI in patients with impaired renal function, including those with end-stage renal disease (ESRD) or those on hemodialysis, have not been studied *[see Use in Specific Populations (8.6)]*.

Hepatic Impairment

The effects of hepatic impairment on the pharmacokinetics of RAVICTI were studied in patients with mild, moderate and severe hepatic impairment of (Child-Pugh class A, B, and C, respectively) receiving 100 mg/kg of RAVICTI twice daily for 7 days.

Plasma glycerol phenylbutyrate was not measured in patients with hepatic impairment.

After multiple doses of RAVICTI in patients with hepatic impairment of Child-Pugh A, B, and C, geometric mean AUC_t of PBA was 42%, 84%, and 50% higher, respectively, while geometric mean AUC_t of PAA was 22%, 53%, and 94% higher, respectively, than in healthy subjects.

In patients with hepatic impairment of Child-Pugh A, B, and C, geometric mean AUC_t of PAGN was 42%, 27%, and 22% lower, respectively, than that in healthy subjects.

The proportion of PBA excreted as PAGN in the urine in Child-Pugh A, B, and C was 80%, 58%, and 85%, respectively, and, in healthy volunteers, was 67%.

In another study in patients with moderate and severe hepatic impairment (Child-Pugh B and C), mean C_{max} of PAA was 144 micrograms/mL (range: 14 to 358 micrograms/mL) after daily dosing of 6 mL of RAVICTI twice daily, while mean C_{max} of PAA was 292 micrograms/mL (range: 57 to 655 micrograms/mL) after daily dosing of 9 mL of RAVICTI twice daily. The ratio of mean C_{max} values for PAA to PAGN among all patients dosed with 6 mL and 9 mL twice daily were 3 and 3.7, respectively.

After multiple doses, a PAA concentration greater than 200 micrograms/mL was associated with a ratio of plasma PAA to PAGN concentrations higher than 2.5 *[see Dosage and Administration (2.5)]*.

Drug Interaction Studies

In vitro PBA or PAA did not induce CYP1A2, suggesting that *in vivo* drug interactions via induction of CYP1A2 is unlikely.

In *in vitro* studies, PBA at a concentration of 800 micrograms/mL caused greater than 60% reversible inhibition of cytochrome P450 isoenzymes CYP2C9, CYP2D6, and CYP3A4/5 (testosterone 6β-hydroxylase activity). The *in vitro* study suggested that *in vivo* drug interactions with substrates of CYP2D6 cannot be ruled out. The inhibition of CYP isoenzymes 1A2, 2C8, 2C19, and 2D6 by PAA at the concentration of 2.8 mg/mL was observed *in vitro*. Clinical implication of these results is unknown.

Effects of RAVICTI on other drugs

Midazolam

In healthy subjects, when oral midazolam was administered after multiple doses of RAVICTI (4 mL three times a day for 3 days) under fed conditions, the mean C_{max} and AUC for

midazolam were 25% and 32% lower, respectively, compared to administration of midazolam alone. In addition, the mean C_{max} and AUC for 1-hydroxy midazolam were 28% and 58% higher, respectively, compared to administration of midazolam alone *[see Drug Interactions (7.3)]*.

Celecoxib

Concomitant administration of RAVICTI did not significantly affect the pharmacokinetics of celecoxib, a substrate of CYP2C9. When 200 mg of celecoxib was orally administered with RAVICTI after multiple doses of RAVICTI (4 mL three times a day for 6 days) under fed conditions (a standard breakfast was consumed 5 minutes after celecoxib administration), the mean C_{max} and AUC for celecoxib were 13% and 8% lower than after administration of celecoxib alone.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In a 2-year study in Sprague-Dawley rats, glycerol phenylbutyrate caused a statistically significant increase in the incidence of pancreatic acinar cell adenoma, carcinoma, and combined adenoma or carcinoma at a dose of 650 mg/kg/day in males (4.7 times the dose of 6.9 mL/m^2/day in adult patients, based on combined AUCs for PBA and PAA) and 900 mg/kg/day in females (8.4 times the dose of 6.9 mL/m^2/day in adult patients, based on combined AUCs for PBA and PAA). The incidence of the following tumors was also increased in female rats at a dose of 900 mg/kg/day: thyroid follicular cell adenoma, carcinoma and combined adenoma or carcinoma, adrenal cortical combined adenoma or carcinoma, uterine endometrial stromal polyp, and combined polyp or sarcoma. The dose of 650 mg/kg/day in male rats is 3 times the dose of 7.5 mL/m^2/day in pediatric patients, based on combined AUCs for PBA and PAA. The dose of 900 mg/kg/day in female rats is 5.5 times the dose of 7.5 mL/m^2/day in pediatric patients, based on combined AUCs for PBA and PAA. In a 26-week study in transgenic (Tg.rasH2) mice, glycerol phenylbutyrate was not tumorigenic at doses up to 1000 mg/kg/day.

Mutagenesis

Glycerol phenylbutyrate was not genotoxic in the Ames test, the *in vitro* chromosomal aberration test in human peripheral blood lymphocytes, or the *in vivo* rat micronucleus test. The metabolites PBA, PAA, PAGN, and phenylacetylglycine were not genotoxic in the Ames test or *in vitro* chromosome aberration test in Chinese hamster ovary cells.

Impairment of Fertility

Glycerol phenylbutyrate had no effect on fertility or reproductive function in male and female rats at oral doses up to 900 mg/kg/day. At doses of 1200 mg/kg/day (approximately 7 times the dose of 6.9 mL/m^2/day in adult patients, based on combined AUCs for PBA and PAA), maternal toxicity was observed and the number of nonviable embryos was increased.

14 CLINICAL STUDIES

14.1 Clinical Studies in Adult Patients with UCDs

Active-Controlled, 4-Week, Noninferiority Study (Study 1)

A randomized, double-blind, active-controlled, crossover, noninferiority study (Study 1) compared RAVICTI to sodium phenylbutyrate by evaluating ammonia levels in patients with UCDs who had been on sodium phenylbutyrate prior to enrollment for control of their UCD. Patients were required to have a confirmed diagnosis of UCD involving deficiencies of CPS, OTC, or ASS, confirmed via enzymatic, biochemical, or genetic testing. Patients had to have no clinical evidence of hyperammonemia at enrollment and were not allowed to receive drugs known to increase ammonia levels (e.g., valproate), increase protein catabolism (e.g., corticosteroids), or significantly affect renal clearance (e.g., probenecid).

The primary endpoint was the 24-hour AUC (a measure of exposure to ammonia over 24 hours) for venous ammonia on days 14 and 28 when the drugs were expected to be at steady state. Statistical noninferiority would be established if the upper limit of the 2-sided 95% CI for the ratio of the geometric means (RAVICTI/sodium phenylbutyrate) for the endpoint was 1.25 or less.

Forty-five patients were randomized 1:1 to 1 of 2 treatment arms to receive either

- Sodium phenylbutyrate for 2 weeks → RAVICTI for 2 weeks; or
- RAVICTI for 2 weeks → sodium phenylbutyrate for 2 weeks.

Sodium phenylbutyrate or RAVICTI were administered three times daily with meals. The dose of RAVICTI was calculated to deliver the same amount of PBA as the sodium phenylbutyrate dose the patients were taking when they entered the study. Forty-four patients received at least 1 dose of RAVICTI in the study.

Patients adhered to a low-protein diet and received amino acid supplements throughout the study. After 2 weeks of dosing, by which time patients had reached steady state on each treatment, all patients had 24 hours of ammonia measurements.

Demographic characteristics of the 45 patients enrolled in Study 1 were as follows: mean age at enrollment was 33 years (range: 18 to 75 years); 69% were female; 33% had adult-onset disease; 89% had OTC deficiency; 7% had ASS deficiency; 4% had CPS deficiency.

RAVICTI was non-inferior to sodium phenylbutyrate with respect to the 24-hour AUC for ammonia. Forty-four patients were evaluated in this analysis. Mean 24-hour AUCs for ammonia during steady-state dosing were 866 micromol•h/L and 977 micromol•h/L with RAVICTI and sodium phenylbutyrate, respectively. The ratio of geometric means was 0.91 [95% CI 0.8, 1.04].

The mean ammonia levels over 24-hours after 2 weeks of dosing (on day 14 and 28) in the double-blind short-term study (Study 1) are displayed in Figure 2 below. The mean and median maximum ammonia levels (C_{max}) over 24 hours and 24-hour AUC for ammonia are summarized in Table 3. Ammonia values across different laboratories were normalized to a common normal range of 9 to 35 micromol/L using the following formula after standardization of the units to micromol/L:

Normalized ammonia (micromol/L) = ammonia readout in micromol/L x (35/ULN of a laboratory reference range specified for each assay)

Figure 2: Ammonia Levels in Adult Patients with UCDs in Short-Term Treatment Study 1

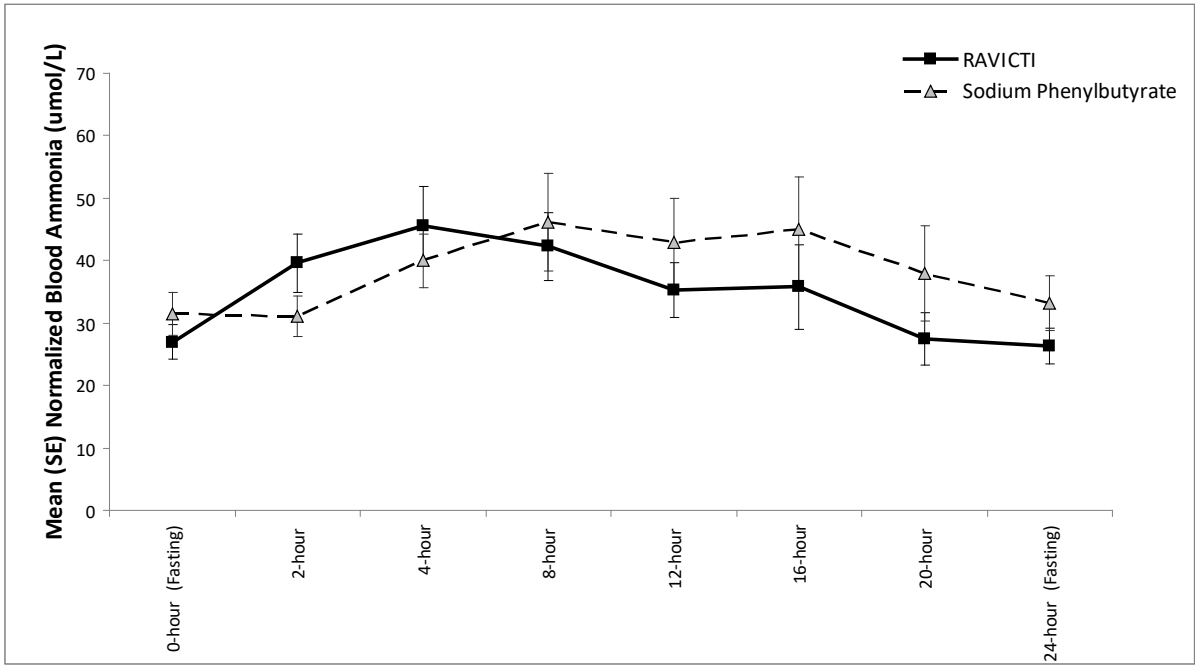


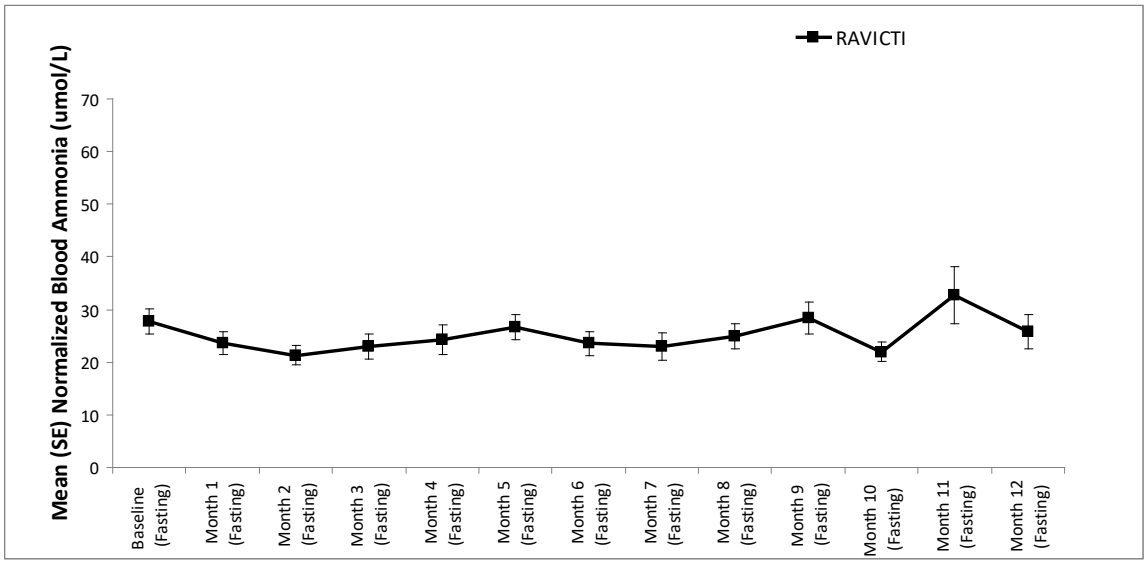
Table 3: Ammonia Levels in Adult Patients with UCDs in Short-Term Treatment Study 1

Timepoint	Ammonia (n=44)	
	Mean (SD)	**Median (min, max)**
Daily C_{max} (micromol/L)		
RAVICTI	61 (46)	51 (12, 245)
Sodium phenylbutyrate	71 (67)	46 (14, 303)
24-Hour AUC (micromol•h/L)		
RAVICTI	866 (661)	673 (206, 3351)
Sodium phenylbutyrate	977 (865)	653 (302, 4666)

Open-Label, Uncontrolled, Extension Study in Adults

A long-term (12-month), uncontrolled, open-label study (Study 2) was conducted to assess monthly ammonia control and hyperammonemic crisis over a 12-month period. A total of 51 adults were in the study and all but 6 had been converted from sodium phenylbutyrate to RAVICTI. Venous ammonia levels were monitored monthly. Mean fasting ammonia values in adults in Study 2 were within normal limits during long-term treatment with RAVICTI (range: 6 to 30 micromol/L). Of 51 adult patients participating in the 12-month, open-label treatment with RAVICTI, 7 patients (14%) reported a total of 10 hyperammonemic crises. The fasting ammonia measured during Study 2 is displayed in Figure 3. Ammonia values across different laboratories were normalized to a common normal range of 9 to 35 micromol/L.

Figure 3: Ammonia Levels in Adult Patients with UCDs in Long-Term Treatment Study 2



Open-Label, Long-Term Study in Adults

An open-label long-term, study (Study 5) was conducted to assess ammonia control in adult patients with UCDs. The study enrolled patients with UCDs who had completed the safety extensions of Study 1, Study 3 or Study 4 (Study 2, 3E and 4E, respectively). A total of 43 adult patients between the ages of 19 and 61 years were in the study. The median length of study participation was 1.9 years (range 0 to 4.5 years). Venous ammonia levels were monitored at a minimum of every 6 months. Mean fasting ammonia values in adult patients in Study 5 were within normal limits during long-term (24 months) treatment with RAVICTI (range: 24.2 to 31.4 micromol/L). Of the 43 adult patients participating in the open-label treatment with RAVICTI, 9 patients (21%) reported a total of 21 hyperammonemic crises. Ammonia values across different laboratories were normalized to a common normal range of 10 to 35 micromol/L.

14.2 Clinical Studies in Pediatric Patients 2 Years to 17 Years of Age with UCDs

The efficacy of RAVICTI in pediatric patients 2 years to 17 years of age with UCDs was evaluated in 2 fixed-sequence, open-label, sodium phenylbutyrate to RAVICTI switchover studies (Studies 3 and 4). Study 3 was 7 days in duration and Study 4 was 10 days in duration.

These studies compared ammonia levels of patients on RAVICTI to ammonia levels of patients on sodium phenylbutyrate in 26 pediatric patients between 2 months and 17 years of age with UCDs. Four patients less than 2 years of age were excluded from this analysis due to insufficient data. The dose of RAVICTI was calculated to deliver the same amount of PBA as the dose of sodium phenylbutyrate that patients were taking when they entered the trial. Sodium phenylbutyrate or RAVICTI were administered in divided doses with meals. Patients adhered to a low-protein diet throughout the study. After a dosing period with each treatment,

all patients underwent 24 hours of venous ammonia measurements, as well as blood and urine pharmacokinetic assessments.

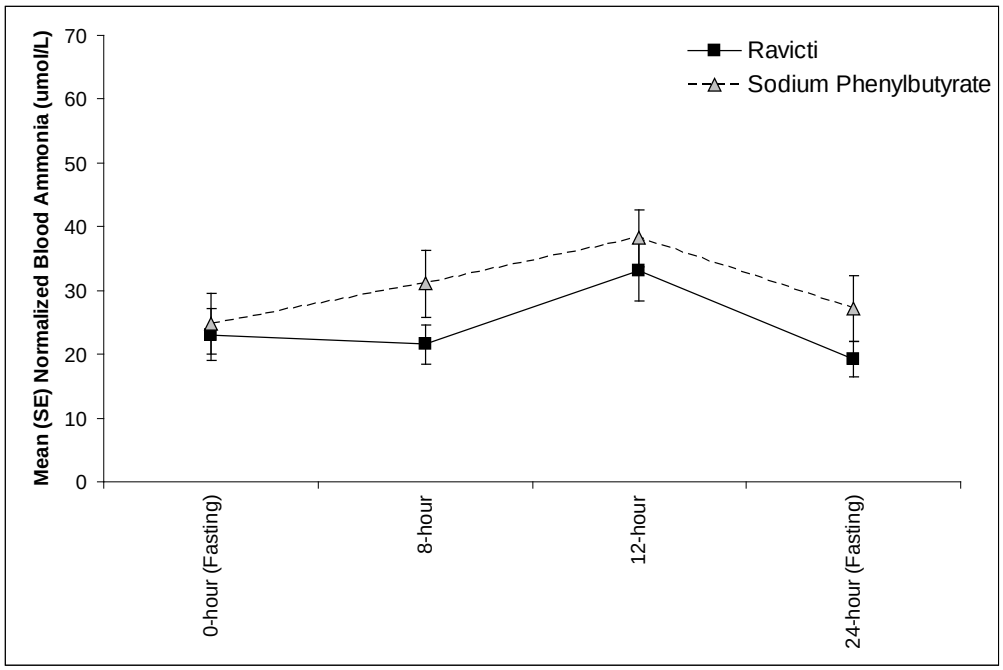
UCD subtypes included OTC (n=12), ASL (n=8), and ASS deficiency (n=2), and patients received a mean RAVICTI dose of 8 mL/m^2/day (8.8 g/m^2/day), with doses ranging from 1.4 to 13.1 mL/m^2/day (1.5 to 14.4 g/m^2/day). Doses in these patients were based on previous dosing of sodium phenylbutyrate.

The 24-hour AUCs for ammonia ($AUC_{0\text{-}24h}$) in 11 pediatric patients 6 years to 17 years of age with UCDs (Study 3) and 11 pediatric patients 2 years to 5 years of age with UCDs (Study 4) were similar between treatments. In pediatric patients 6 years to 17 years of age, the ammonia $AUC_{0\text{-}24h}$ was 604 micromol•h/L vs 815 micromol•h/L on RAVICTI vs sodium phenylbutyrate, respectively. In patients between 2 years and 5 years of age with UCDs, the ammonia $AUC_{0\text{-}24h}$ was 632 micromol•h/L vs 720 micromol•h/L on RAVICTI versus sodium phenylbutyrate, respectively.

The mean ammonia levels over 24 hours in open-label, short-term Studies 3 and 4 at common time points are displayed in Figure 4. Ammonia values across different laboratories were normalized to a common normal range of 9 to 35 micromol/L using the following formula after standardization of the units to micromol/L:

Normalized ammonia (micromol/L) = ammonia readout in micromol/L x (35/ULN of a laboratory reference range specified for each assay)

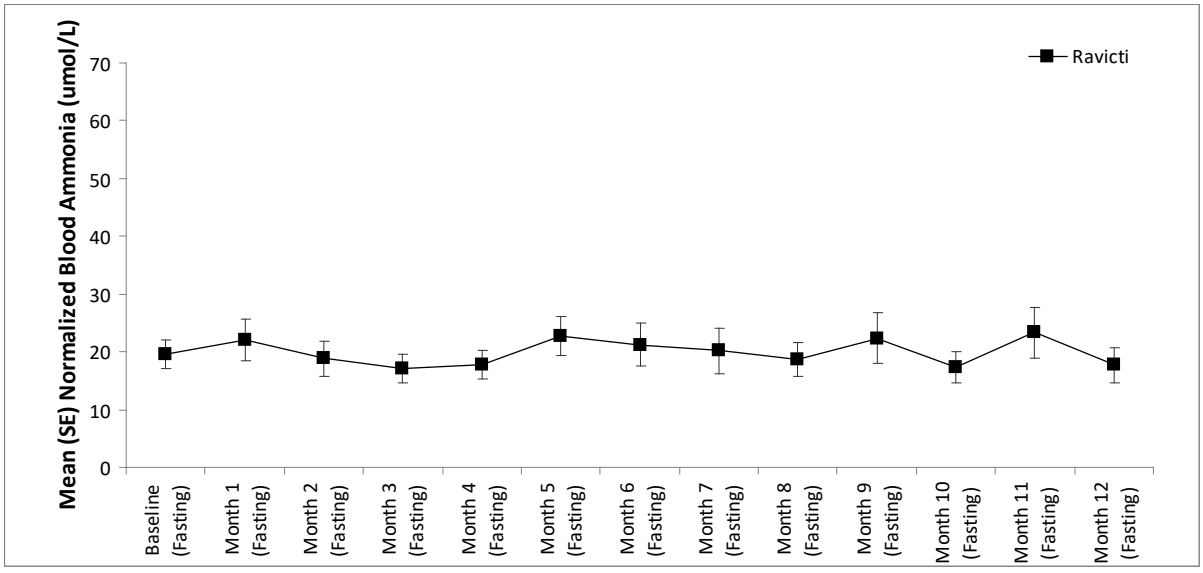
Figure 4: Ammonia Levels in Pediatric Patients 2 Years to 17 Years of Age with UCDs in Short-Term Treatment Studies 3 and 4



Open-Label, Uncontrolled, Extension Studies in Pediatric Patients 2 Years to 17 Years of Age

Long-term (12-month), uncontrolled, open-label studies were conducted to assess monthly ammonia control and hyperammonemic crises over a 12-month period. In two studies (Study 2, which also enrolled adults, and an extension of Study 3, referred to here as Study 3E), a total of 26 pediatric patients ages 6 years to 17 years were enrolled and all but 1 had been converted from sodium phenylbutyrate to RAVICTI. Mean fasting venous ammonia levels were within normal limits (range 17 to 23 micromol/L) during long-term treatment with RAVICTI. Of the 26 pediatric patients 6 years to 17 years of age participating in these two trials, 5 patients (19%) reported a total of 5 hyperammonemic crises. The fasting ammonia levels measured during these two extension studies in patients 6 years to 17 years are displayed in Figure 5. Ammonia values across different laboratories were normalized to a common normal range of 9 to 35 micromol/L.

Figure 5: Ammonia Levels in Pediatric Patients 2 Years to 17 Years of Age with UCDs in Long-Term Treatment Studies 2 and 3E



In an extension of Study 4 (referred to as Study 4E), after a median time on study of 4.5 months (range: 1 to 5.7 months), 2 of 16 pediatric patients ages 2 years to 5 years had experienced three hyperammonemic crises.

Open-Label, Long-Term Study in Pediatric Patients 1 Year to 17 Years of Age

An open-label, long-term study (Study 5) was conducted to assess ammonia levels in pediatric patients with UCD. The study enrolled patients with UCDs who had completed Studies 2, 3E and 4E. A total of 45 pediatric patients ages 1 year to 17 years were included in the study. The median length of treatment was 1.7 years (range 0.2 to 4.6 years). Venous ammonia levels were monitored at a minimum every 6 months. Mean ammonia values in pediatric patients in Study 5 were within normal limits during long-term (24 months) treatment with RAVICTI (range: 15.4 to 25.1 micromol/L). Of the 45 pediatric patients participating in the open-label treatment with RAVICTI, 11 patients (24%) reported a total of

22 hyperammonemic crises. Ammonia values across different laboratories were normalized to a common normal range of 10 to 35 micromol/L.

14.3 Clinical Studies in Pediatric Patients Less Than 2 Years of Age with UCDs

The efficacy of RAVICTI in pediatric patients less than 2 years of age with UCDs was evaluated in uncontrolled, open label studies (Studies 4/4E, 5 *[see Clinical Studies (14.2)]* and 6). A total of 17 pediatric patients with UCDs aged 2 months to less than 2 years participated in Studies 4/4E, 5 and 6. Study 6 enrolled 16 pediatric patients less than 2 months of age.

Uncontrolled, Open-Label Studies in Pediatric Patients Aged 2 Months to Less than 2 Years of Age (Studies 4/4E, 5)

A total of 7 patients with UCDs aged 2 months to less than 2 years participated in Studies 4/4E and 5. In these studies, there were 7, 6, 6, 6 and 3 pediatric patients who completed 1, 6, 9, 12 and 18 months, respectively (mean and median exposure of 15 and 17 months, respectively). Patients were converted from sodium phenylbutyrate to RAVICTI. The dosage of RAVICTI was calculated to deliver the same amount of PBA as the sodium phenylbutyrate dosage the patients were taking when they entered the study.

Patients received a mean RAVICTI dose of 7.5 mL/m^2/day (8.2 g/m^2/day), with doses ranging from 3.3 to 12.3 mL/m^2/day (3.7 to 13.5 g/m^2/day). Patients were dosed three times per day (n=3) or four times per day (n = 4).

Venous ammonia levels were monitored on days 1, 3, and 10 in Study 4 and at week 1 in Study 4E. Two patients had elevated ammonia values on day 1 of treatment (122 micromol/L and 111 micromol/L respectively) and neither had associated signs and symptoms of hyperammonemia. At day 10/week 1, six of the 7 patients had normal ammonia levels (less than 100 micromol/L) while the remaining patient had an elevated ammonia value on day 10 (168 micromol/L) and was asymptomatic.

During the extension period, venous ammonia levels were monitored monthly. Ammonia values across different laboratories were normalized (transformed) to a common normal pediatric range of 28 to 57 micromol/L for comparability. The mean ammonia levels in pediatric patients at month 1, 3, 6, 9 and 12 were 58, 49, 34, 65, and 31 micromol/L during treatment with RAVICTI, respectively.

Three patients reported a total of 3 hyperammonemic crises defined as having signs and symptoms consistent with hyperammonemia (such as frequent vomiting, nausea, headache, lethargy, irritability, combativeness, and/or somnolence) associated with high ammonia levels (greater than 100 micromol/L) and requiring medical intervention. Hyperammonemic crises were precipitated by gastroenteritis, vomiting, infection or no precipitating event (one patient). There were 4 patients who had one ammonia level that exceeded 100 micromol/L which was not associated with a hyperammonemic crisis.

Uncontrolled, Open-Label Study in Pediatric Patients Less Than 2 Years of Age (Study 6)

Study 6 was an uncontrolled, open label study in pediatric patients less than 2 years of age. The primary efficacy endpoint was successful transition to RAVICTI within a period of 4

days followed by 3 days of observation for a total of 7 days, where successful transition was defined as no signs and symptoms of hyperammonemia and a venous ammonia level less than 100 micromol/L. Ammonia levels were monitored for up to 4 days during transition and on day 7.

Pediatric Patients 2 Months to Less than 2 Years of Age

A total of 10 pediatric patients with UCDs aged 2 months to less than 2 years participated in Study 6, of which 6 patients converted from sodium phenylbutyrate to RAVICTI and 1 patient converted from sodium phenyl butyrate and sodium benzoate. The dosage of RAVICTI was calculated to deliver the same amount of PBA as the sodium phenylbutyrate dosage the patients were taking when they entered the trial. Two patients were treatment-naïve and received RAVICTI dosage of 7.5 mL/m^2/day and 9.4 mL/m^2/day, respectively. One additional patient was gradually discontinued from intravenous sodium benzoate and sodium phenylacetate while RAVICTI was initiated. The dosage of RAVICTI after transition was 8.5 mL/m^2/day.

There were 9, 7, 7, 4, 1 and 4 pediatric patients who completed 1, 3, 6, 12, 18 and 24 months, respectively (mean and median exposure of 9 and 9 months, respectively).

Patients received a mean RAVICTI dose of 8 mL/m^2/day (8.8 g/m^2/day), with doses ranging from 4.8 to 11.5 mL/m^2/day (5.3 to 12.6 g/m^2/day). Patients were dosed three times a day (n=6), four times a day (n = 2), or five or more times a day (n=2).

Nine patients successfully transitioned as defined by the primary endpoint. One additional patient developed hyperammonemia on day 3 of dosing and experienced surgical complications (bowel perforation and peritonitis) following jejunal tube placement on day 4. This patient developed hyperammonemic crisis on day 6, and subsequently died of sepsis from peritonitis unrelated to drug. Although two patients had day 7 ammonia values of 150 micromol/L and 111 micromol/L respectively, neither had associated signs and symptoms of hyperammonemia.

During the extension phase, venous ammonia levels were monitored monthly. Ammonia values across different laboratories were normalized (transformed) to a common normal pediatric range of 28 to 57 micromol/L for comparability. The mean normalized ammonia levels in pediatric patients at months 1, 2, 3, 4, 5, 6, 9, 12, 15, 18 and 24 were 67, 53, 78, 93, 78, 67, 38, 38, 36, 48 and 53 micromol/L during treatment with RAVICTI, respectively. Three patients reported a total of 7 hyperammonemic crises as defined in Study 4/4E and 5. Hyperammonemic crises were precipitated by vomiting, upper respiratory tract infection, gastroenteritis, decreased caloric intake or had no identified precipitating event (3 events). There was one additional patient who had one ammonia level that exceeded 100 micromol/L which was not associated with a hyperammonemic crisis.

Pediatric Patients Less than 2 Months of Age

A total of 16 pediatric patients less than 2 months of age participated in Study 6. Median age at enrollment was 0.5 months (range: 0.1 to 2 months). Eight patients had OTC deficiency, 7 patients had ASS deficiency, and 1 patient had ASL deficiency. Ten of the 16 patients transitioned from sodium phenylbutyrate to RAVICTI within 3 days of treatment and their initial dosage of RAVICTI was calculated to deliver the same amount of phenylbutyrate as

the sodium phenylbutyrate dosage administered prior to RAVICTI dosing. Three of the 16 patients were treatment-naïve and started RAVICTI at dosages of 9, 9.4, and 9.6 mL/m^2/day. The remaining 3 of the 16 patients transitioned from intravenous sodium benzoate and sodium phenylacetate to RAVICTI within 3 days of treatment and their initial dosages of RAVICTI were 10.4, 10.9, and 10.9 mL/m^2/day.

Of the 16 patients, 16, 14, 12, 6, and 3 patients were treated for 1, 3, 6, 12, and 18 months, respectively.

After the initial 7-day transition period, patients received a mean RAVICTI dosage of 8 mL/m^2/day (8.8 g/m^2/day), with doses ranging from 3.1 to 12.7 mL/m^2/day (3.4 to 14 g/m^2/day). The frequency of dosing varied throughout the study. The majority of patients were dosed three times per day with feeding. No patients discontinued during the 7-day transition phase. Ammonia values across different laboratories were normalized (transformed) to a common normal pediatric range of 28 to 57 micromol/L for comparability.

During the safety extension phase (months 1-24), venous ammonia levels were monitored monthly for the first 6 months of treatment and every 3 months thereafter until the patients terminated or completed the study. During the safety extension phase, 1 patient discontinued from the study due to an adverse event (increased hepatic enzymes), 2 patients were withdrawn from the study by their parent/guardian, and 4 patients discontinued from the study early to undergo a liver transplant (protocol-defined discontinuation criterion). The normalized ammonia levels in pediatric patients with available values (which varied by month of treatment) in Study 6 in patients less than 2 months of age are shown in Table 4.

Table 4: Ammonia* Levels in Pediatric Patients Less than 2 Months of Age with UCDs in Study 6

Month	N (patients with available ammonia level)	Normalized Ammonia (micromol/L)**	
		Mean (SD)	Median (Min, Max)
1	15	71 (52)	60 (18, 227)
2	11	58 (40)	50 (16, 168)
3	14	53 (34)	46 (11, 122)
4	11	94 (106)	64 (35, 407)
5	10	52 (18)	57 (27, 86)
6	9	49 (24)	42 (22, 91)
9	8	56 (34)	45 (22, 122)
12	6	35 (17)	36 (11, 60)
15	4	52 (12)	52 (39, 67)
18	3	64 (14)	63 (50, 78)
24	9	63 (29)	72 (23, 106)

*normalized ammonia (micromol/L) = ammonia readout in micromol/L x (35/ULN of a laboratory reference range specified for each assay)
**normal range: 28 to 57 micromol/L.

Five patients (all less than 1 month of age) experienced a total of 7 hyperammonemic crises defined as in Study 4/4E and 5. Hyperammonemic crises were precipitated by upper respiratory tract infection (2 events), change in diet (1 event), or had no identified precipitating event (4 events).

16 HOW SUPPLIED/STORAGE AND HANDLING

RAVICTI® (glycerol phenylbutyrate) oral liquid 1.1 g/mL is supplied in multi-use, 25-mL glass bottles. The bottles are supplied in the following configurations:

- NDC 75987-050-06: Single 25-mL bottle per carton
- NDC 75987-050-07: Four 25-mL bottles per carton

Store at 20°-25°C (68°-77°F) with excursions permitted to 15°-30°C (59°-86°F). Discard bottle 28 days after opening.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Neurotoxicity *[see Warnings and Precautions (5.1)].*

- Inform patients/caregivers that adverse reactions of RAVICTI are sometimes the same as symptoms of high blood ammonia. Neurological adverse reactions may also be associated with the major metabolite of RAVICTI, PAA, and may be reversible. Blood tests for PAA may be done to measure the amount of PAA in the blood. Instruct the patient/caregiver to contact the healthcare provider immediately if the patient experiences: nausea, vomiting, headache, fatigue, somnolence, lightheadedness, confusion, exacerbation of preexisting neuropathy, disorientation, impaired memory, dysgeusia, or hypoacusis.

Pregnancy

Report pregnancies to Horizon at 1-866-479-6742 *[see Use in Specific Populations (8.1)]*.

Lactation

Advise patients that breastfeeding is not recommended during treatment with RAVICTI *[see Use in Specific Populations (8.2)]*.

Administration

- Instruct patients to take RAVICTI with food or formula and to administer directly into the mouth via oral syringe.
- Instruct patients to use the RAVICTI bottle and oral syringe as follows:
  - Use a new reclosable bottle cap adapter with each new bottle that is opened.
  - Open the RAVICTI bottle and twist on the new reclosable bottle cap adapter.
  - Use a new and dry oral syringe to withdraw each prescribed dose of RAVICTI.

- Discard the oral syringe after each dose.
- Tightly close the tethered tab on the reclosable bottle cap adapter after each use.
- Do not rinse the reclosable bottle cap adapter.
- Discard bottle and any remaining contents 28 days after opening.
- If water or moisture enters the RAVICTI bottle, the contents will become cloudy in appearance. If the contents of the bottle appear cloudy at any time, do not use the remaining RAVICTI in the bottle and return it to the pharmacy to be discarded.

- Instruct that RAVICTI should be administered just prior to breastfeeding in infants who are breastfeeding.
- Instruct patients to take RAVICTI orally, even if they have a nasogastric and/or gastrostomy tube. For patients who cannot swallow and who have a nasogastric tube or gastrostomy tube in place, instruct patients/caregivers to administer RAVICTI as follows:
  - Utilize a new dry oral syringe to withdraw the prescribed dosage of RAVICTI from the bottle.
  - Place the tip of the syringe into the gastrostomy/nasogastric tube.
  - Utilizing the plunger of the syringe, administer RAVICTI into the tube.
  - Use a separate syringe to flush the nasogastric/gastrostomy tube. Flush once with 10 mL of water or formula and allow the flush to drain.
  - If needed, flush a second time with an additional 10 mL of water or formula to clear the tube.

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

RAV-US-PI-001

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 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.

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 all of your medical conditions, including 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. If you become pregnant during treatment with RAVICTI, call Horizon at 1-866-479-6742 to report the pregnancy.
- 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.
- In an infant who is breastfeeding, give RAVICTI just before breastfeeding.
- RAVICTI is an oral liquid that is taken by mouth using an oral syringe.
- Ask your pharmacist for oral syringes and a reclosable bottle cap adapter for each bottle you receive if you do not have them.
- Use the RAVICTI bottle and oral syringe as follows:
  - Use a new reclosable bottle cap adapter with each new RAVICTI bottle that is opened.
  - Open the RAVICTI bottle and twist on the new reclosable bottle cap adapter.
  - Use a new dry oral syringe to remove each prescribed dose of RAVICTI.
  - Throw away (discard) the oral syringe after each dose.
  - Tightly close the tethered tab on the reclosable bottle cap adapter after each use.
  - Do not rinse the reclosable bottle cap adapter.
  - If water or moisture enters the RAVICTI bottle, the contents will become cloudy in appearance. If the contents appear cloudy at any time, **do not** use the remaining RAVICTI and return the bottle to your pharmacy to throw it away.
  - Throw away the bottle and any unused RAVICTI 28 days after opening.
- 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 a new dry oral syringe to withdraw each 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.
- Use a separate syringe to flush the nasogastric or gastrostomy 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
- constipation
- diarrhea
- fever
- reduced food intake
- cough
- stuffy nose
- runny nose
- skin rash
- small round bumps on the skin

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

- vomiting
- rash
- gastroesophageal reflux
- increased levels of liver enzymes in the blood
- decreased appetite and reduced food intake
- low red blood cell count (anemia)
- cough
- loss of too much body fluid (dehydration)
- too much acid in the blood (acidosis)
- high blood platelet count (thrombocytosis)
- low blood platelet count (thrombocytopenia)
- low blood neutrophil count (type of white blood cell) (neutropenia)
- high blood white blood cell count (lymphocytosis)
- diarrhea
- gas
- constipation
- fever
- drowsiness (lethargy)
- irritability
- agitation

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.

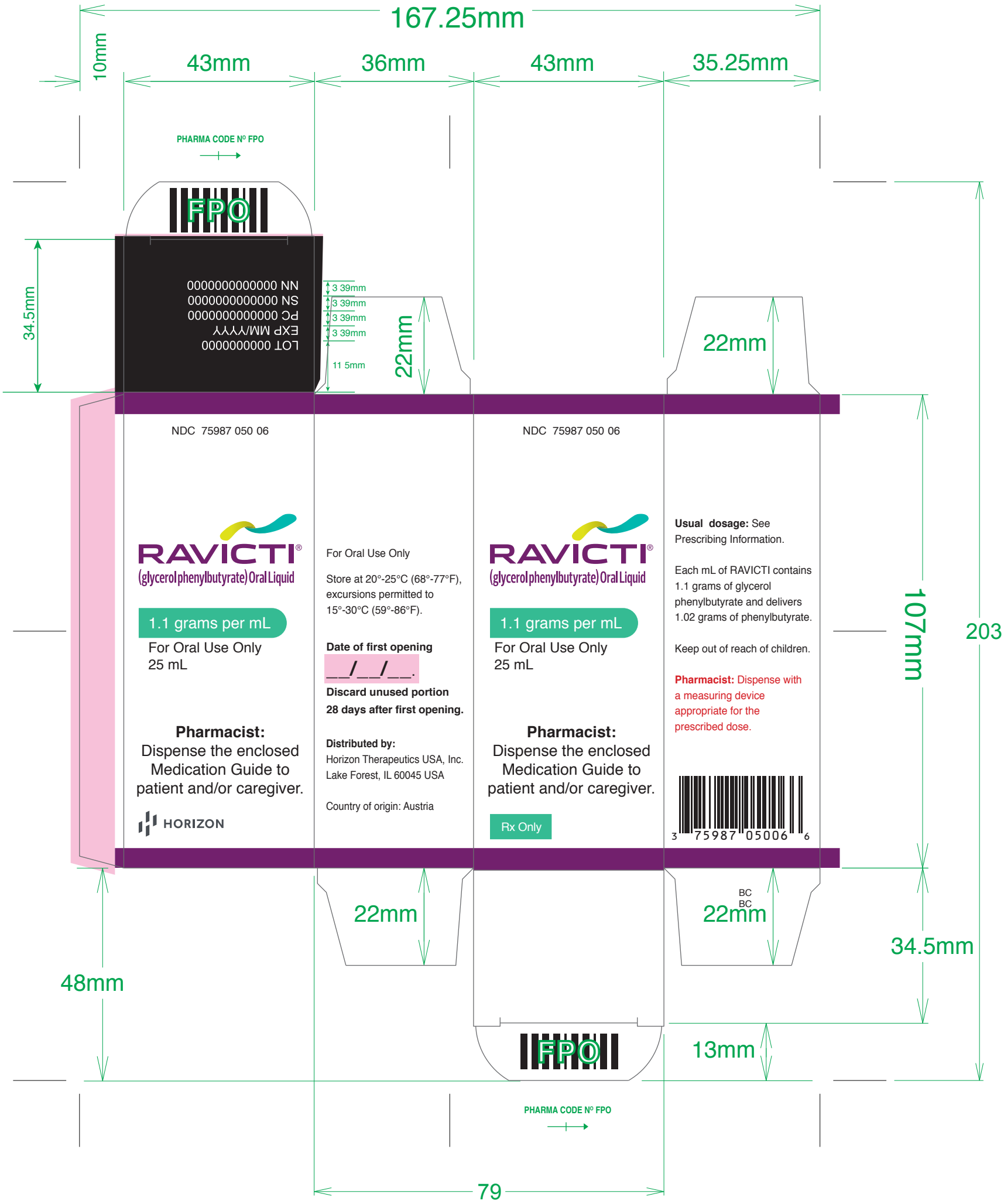
What are the ingredients in RAVICTI?

Active ingredient: glycerol phenylbutyrate

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

For more information, go to www.RAVICTI.com or call 1-866-479-6742.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: September 2021



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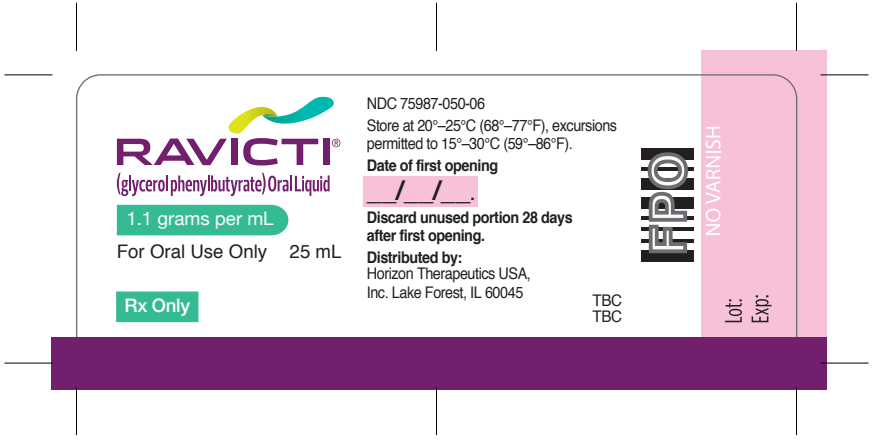

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Proposed Package Insert

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

Dosage and Administration (2.1, 2.6) 9/2021

INDICATIONS AND USAGE

RAVICTI is a nitrogen-binding agent indicated 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. (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, 8.7)

DOSAGE FORMS AND STRENGTHS

Oral liquid: 1.1 g/mL. (3)

CONTRAINDICATIONS

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)
- 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 LifeScience Logistics at 1-855-738-6171 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: 9/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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 (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.
- Instruct patients to use the RAVICTI bottle and oral syringe as follows:
  - Use a new reclosable bottle cap adapter with each new bottle that is opened.
  - Open the RAVICTI bottle and twist on the new reclosable bottle cap adapter.
  - Use a new and dry oral syringe to withdraw each prescribed dose of RAVICTI.
  - Discard the oral syringe after each dose.
  - Tightly close the tethered tab on the reclosable bottle cap adapter after each use.
  - Do not rinse the reclosable bottle cap adapter.
  - Discard bottle and any remaining contents 28 days after opening.
  - If water or moisture enters the RAVICTI bottle, the contents will become cloudy in appearance. If the contents of the bottle appear cloudy at any time, do not use the remaining RAVICTI in the bottle and return it to the pharmacy to be discarded.
- Instruct that RAVICTI should be administered just prior to breastfeeding in infants who are breastfeeding.
- 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 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 plasma ammonia levels during treatment with RAVICTI and when changing the dosage of RAVICTI.

The methods used for measuring plasma ammonia levels vary among individual laboratories and values obtained using different assay methods may not be interchangeable. Normal ranges and therapeutic target levels for plasma ammonia depend upon the assay method used

by the individual laboratory. During treatment with RAVICTI, refer to the assay-specific normal ranges and to the therapeutic target ranges for plasma ammonia.

Normal Plasma Ammonia

In patients treated with RAVICTI who experience neurologic symptoms (e.g. nausea, vomiting, headache, somnolence or confusion) in the absence of high plasma ammonia or other intercurrent illness to explain these symptoms, consider reducing the RAVICTI dosage and clinically monitor patients for potential neurotoxicity from high phenylacetate (PAA) concentrations. If available, obtain measurements of plasma PAA concentrations and plasma phenylacetylglutamine (PAGN) to calculate the ratio of plasma PAA to PAGN which may help to guide RAVICTI dosing. The PAA to PAGN ratio has generally been less than 1 in patients with UCDs who did not have significant plasma PAA accumulation. In general, a high PAA to PAGN ratio may indicate a slower or less efficient conjugation reaction to form PAGN, which may lead to increases in PAA without further conversion to PAGN *[see Warnings and Precautions (5.1), Clinical Pharmacology (12.3)]*.

Elevated Plasma Ammonia

In patients 6 years and older, when plasma ammonia is elevated, increase the RAVICTI dosage to maintain fasting plasma ammonia to less than half the upper limit of normal (ULN). 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. If available, the ratio of PAA to PAGN in the same plasma sample may provide additional information to assist in dosage adjustment decisions *[see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]*.

Dietary Protein Intake

If available, urinary phenylacetylglutamine (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 insufficient to cover daily dietary protein intake and the fasting ammonia is greater than half the ULN, the RAVICTI dosage should be increased. The amount of dosage adjustment should factor in the amount of dietary protein that has not been covered, as indicated by the 24-hour U-PAGN output, 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)]*.

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 recommended dosing range (4.5 mL/m^2/day) and the dosage should be kept at the lowest necessary to control the patient's plasma ammonia *[see Use in Specific Populations (8.7)]*.

2.6 Preparation for Nasogastric Tube or Gastrostomy Tube Administration

It is recommended that all patients who can swallow take RAVICTI orally, even those with nasogastric and/or gastrostomy tubes. For patients who cannot swallow, a nasogastric tube or gastrostomy tube may be used to administer RAVICTI as follows:

- Utilize a new dry oral syringe to withdraw each prescribed dosage of RAVICTI from the bottle.
- Place the tip of the syringe into the nasogastric/gastrostomy tube.
- Utilizing the plunger of the syringe, administer RAVICTI into the tube.
- Use a separate syringe to flush the nasogastric/gastrostomy tube. Flush once with 10 mL of water or formula and allow the flush to drain.
- If needed, flush a second time with an additional 10 mL of water or formula to clear the tube.

For 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. Therefore, these patients should be closely monitored using ammonia levels following initiation of RAVICTI dosing or dosage adjustments.

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 with known hypersensitivity to phenylbutyrate. Signs of hypersensitivity include wheezing, dyspnea, coughing, hypotension, flushing, nausea, and rash.

5 WARNINGS AND PRECAUTIONS

5.1 Neurotoxicity

Increased exposure to PAA, the major metabolite of RAVICTI, may be associated with neurotoxicity in patients with UCDs. In a study of adult cancer patients, subjects received sodium phenylacetate administered as a 1-hour infusion twice daily at two dose levels of 125 and 150 mg/kg for a 2-week period. Of 18 subjects enrolled, 7 had a history of primary central nervous system tumor. Signs and symptoms of potential PAA neurotoxicity, which were reversible, were reported at plasma PAA concentrations above 500 micrograms/mL and included somnolence, fatigue, lightheadedness, headache, dysgeusia, hypoacusis,

disorientation, impaired memory, and exacerbation of preexisting neuropathy. PAA concentrations were not measured when symptoms resolved.

In healthy subjects, after administration of 4 mL and 6 mL RAVICTI 3 times daily (13.2 g/day and 19.8 g/day, respectively) for 3 days, a dose-dependent increase in non-serious nervous system adverse reactions were observed. In subjects who had nervous system adverse reactions, plasma PAA concentrations, which were measured on Day 3 per protocol and not always at onset of symptoms, ranged from 8 to 56 micrograms/mL with 4 mL RAVICTI 3 times daily and from 31 to 242 micrograms/mL with 6 mL RAVICTI 3 times daily.

In clinical trials in patients with UCDs who had been on sodium phenylbutyrate prior to administration of RAVICTI, adverse reactions of headache, fatigue, symptoms of peripheral neuropathy, seizures, tremor and/or dizziness were reported. No correlation between plasma PAA concentration and neurologic symptoms was identified but plasma PAA concentrations were generally not consistently measured at the time of neurologic symptom occurrence *[see Clinical Pharmacology (12.3)]*.

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 *[see Dosage and Administration (2.4)]*.

5.2 Pancreatic Insufficiency or Intestinal Malabsorption

Exocrine pancreatic enzymes hydrolyze RAVICTI in the small intestine, separating the active moiety, phenylbutyrate, from glycerol. This process allows phenylbutyrate to be absorbed into the circulation. 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 in patients with pancreatic insufficiency or intestinal malabsorption.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Neurotoxicity *[see Warnings and Precautions (5.1)]*
- Pancreatic insufficiency or Intestinal Malabsorption *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Assessment of adverse reactions was based on exposure of 45 adult patients (31 female and 14 male) with UCD subtype deficiencies of ornithine transcarbamylase (OTC, n=40), carbamoyl phosphate synthetase (CPS, n=2), and argininosuccinate synthetase (ASS, n=1) in

a randomized, double-blind, active-controlled (RAVICTI vs sodium phenylbutyrate), crossover, 4-week study (Study 1) that enrolled patients 18 years of age and older *[see Clinical Studies (14.1)]*. One of the 45 patients received only sodium phenylbutyrate prior to withdrawing on day 1 of the study due to an adverse reaction.

The most common adverse reactions (occurring in at least 10% of patients) reported during short-term treatment with RAVICTI were diarrhea, flatulence, and headache. Table 1 summarizes adverse reactions occurring in 2 or more patients treated with RAVICTI or sodium phenylbutyrate (incidence of at least 4% in either treatment arm).

Table 1: Adverse Reactions Reported in 2 or More Adult Patients with UCDs (at least 4% in Either Treatment Arm) in Study 1

	Number (%) of Patients in Study 1	
	Sodium Phenylbutyrate (N = 45)	**RAVICTI (N = 44)**
Diarrhea	3 (7)	7 (16)
Headache	4 (9)	6 (14)
Flatulence	1 (2)	6 (14)
Abdominal pain	2 (4)	3 (7)
Vomiting	2 (4)	3 (7)
Decreased appetite	2 (4)	3 (7)
Fatigue	1 (2)	3 (7)
Dyspepsia	3 (7)	2 (5)
Nausea	3 (7)	1 (2)
Dizziness	4 (9)	0
Abdominal discomfort	3 (7)	0

Other Adverse Reactions

RAVICTI has been evaluated in 77 patients with UCDs (51 adult and 26 pediatric patients ages 2 years to 17 years) in 2 open-label long-term studies, in which 69 patients completed 12 months of treatment with RAVICTI (median exposure = 51 weeks). During these studies there were no deaths.

Adverse reactions reported in at least 10% of adult patients were nausea, vomiting, diarrhea, decreased appetite, dizziness, headache, and fatigue.

Adverse reactions reported in at least 10% of pediatric patients ages 2 years to 17 years were upper abdominal pain, rash, nausea, vomiting, diarrhea, decreased appetite, and headache.

RAVICTI has been evaluated in 17 patients with UCDs ages 2 months to less than 2 years in 3 open-label studies. The median exposure was 6 months (range 0.2 to 20 months). Adverse reactions reported in at least 10% of pediatric patients aged 2 months to less than 2 years were neutropenia, vomiting, constipation, diarrhea, pyrexia, hypophagia, cough, nasal congestion, rhinorrhea, rash, and papule.

RAVICTI has been evaluated in 16 patients with UCDs less than 2 months of age (age range 0.1 to 2 months, median age 0.5 months) in a single, open-label study. The median exposure was 10 months (range 2 to 20 months). Adverse reactions reported in at least 10% of pediatric patients aged less than 2 months were 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.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of RAVICTI. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

- Abnormal body odor, including from skin, hair and urine
- Retching and gagging
- Dysgeusia or burning sensation in mouth

7 DRUG INTERACTIONS

7.1 Potential for Other Drugs to Affect Ammonia

Corticosteroids

Use of corticosteroids may cause the breakdown of body protein and increase plasma ammonia levels. Monitor ammonia levels closely when corticosteroids and RAVICTI are used concomitantly.

Valproic Acid and Haloperidol

Hyperammonemia may be induced by haloperidol and by valproic acid. Monitor ammonia levels closely when use of valproic acid or haloperidol is necessary in patients with UCDs.

7.2 Potential for Other Drugs to Affect RAVICTI

Probenecid

Probenecid may inhibit the renal excretion of metabolites of RAVICTI including PAGN and PAA.

7.3 Potential for RAVICTI to Affect Other Drugs

Drugs with narrow therapeutic index that are substrates of CYP3A4

RAVICTI is a weak inducer of CYP3A4 in humans. Concomitant use of RAVICTI may decrease the systemic exposure to drugs that are substrates of CYP3A4. Monitor for decreased efficacy of drugs with narrow therapeutic index (e.g., alfentanil, quinidine, cyclosporine) *[see Clinical Pharmacology (12.3)]*.

Midazolam

Concomitant use of RAVICTI decreased the systemic exposure of midazolam. Monitor for suboptimal effect of midazolam in patients who are being treated with RAVICTI.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited available data with RAVICTI use in pregnant women are insufficient to inform a drug-associated risk of major birth defects and miscarriage. In an animal reproduction study, administration of oral glycerol phenylbutyrate to pregnant rabbits during organogenesis at doses up to 2.7–times the dose of 6.87 mL/m^2/day in adult patients resulted in maternal toxicity, but had no effects on embryo-fetal development. In addition, there were no adverse developmental effects with administration of oral glycerol phenylbutyrate to pregnant rats during organogenesis at 1.9 times the dose of 6.87 mL/m^2/day in adult patients; however, maternal toxicity, reduced fetal weights, and variations in skeletal development were observed in pregnant rats administered oral glycerol phenylbutyrate during organogenesis at doses greater than or equal to 5.7 times the dose of 6.87 mL/m^2/day in adult patients *[*see *Data]*. Report pregnancies to Horizon at 1-866-479-6742.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

Oral administration of glycerol phenylbutyrate during the period of organogenesis up to 350 mg/kg/day in rabbits produced maternal toxicity, but no effects on embryo-fetal development. The dose of 350 mg/kg/day in rabbits is approximately 2.7 times the dose of 6.87 mL/m^2/day in adult patients, based on combined area under the plasma concentration-time curve [AUCs] for PBA and PAA. In rats, at an oral dose of 300 mg/kg/day of glycerol phenylbutyrate (1.9 times the dose of 6.87 mL/m^2/day in adult patients, based on combined AUCs for PBA and PAA) during the period of organogenesis, no effects on embryo-fetal development were observed. Doses of 650 mg/kg/day or greater produced maternal toxicity and adverse effects on embryo-fetal development including reduced fetal weights and cervical ribs at the 7th cervical vertebra. The dose of 650 mg/kg/day in rats is approximately 5.7 times the dose of 6.87 mL/m^2/day in adult patients, based on combined AUCs for PBA and PAA. No developmental abnormalities, effects on growth, or effects on learning and memory were observed through maturation of offspring following oral administration in pregnant rats with up to 900 mg/kg/day of glycerol phenylbutyrate (8.5 times the dose of 6.87 mL/m^2/day in adult patients, based on combined AUCs for PBA and PAA) during organogenesis and lactation.

8.2 Lactation

Risk Summary

There are no data on the presence of RAVICTI in human milk, the effects on the breastfed infant, or the effects on milk production. Because of the potential for serious adverse reactions, including neurotoxicity and tumorigenicity in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with RAVICTI.

8.4 Pediatric Use

Patients 2 Years to 17 Years of Age

The safety and effectiveness of RAVICTI in patients 2 years to less than 18 years of age have been established in 3 clinical studies: 2 open-label, fixed-sequence, switchover clinical studies from sodium phenylbutyrate to RAVICTI, and 1 long-term, open label safety study *[see Adverse Reactions (6.1), Clinical Studies (14.2)]*.

Patients Less Than 2 Years of Age

The safety and effectiveness of RAVICTI in patients with UCDs less than 2 years of age have been established in 3 open-label studies. Pharmacokinetics and pharmacodynamics (plasma ammonia), and safety were studied in 17 patients aged 2 months to less than 2 years of age and in 16 patients less than 2 months of age *[see Adverse Reactions (6.1), Clinical Studies (14.3)]*.

Juvenile Animal Toxicity Data

In a juvenile rat study with daily oral dosing performed on postpartum day 2 through mating and pregnancy after maturation, terminal body weight was dose-dependently reduced by up to 16% in males and 12% in females at 900 mg/kg/day or higher (3 times the dose of 6.87 mL/m^2/day in adult patients, based on combined AUCs for PBA and PAA). Learning, memory, and motor activity endpoints were not affected. However, fertility (number of pregnant rats) was decreased by up to 25% at 650 mg/kg/day or higher (2.6 times the dose of 6.87 mL/m^2/day in adult patients, based on combined AUCs for PBA and PAA).

8.5 Geriatric Use

Clinical studies of RAVICTI did not include sufficient numbers of subjects 65 years of age and older to determine whether they respond differently than younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Renal Impairment

The efficacy and safety of RAVICTI in patients with renal impairment are unknown. Monitor ammonia levels closely when starting patients with impaired renal function on RAVICTI.

8.7 Hepatic Impairment

No studies were conducted in patients with UCDs and hepatic impairment. Because conversion of PAA to PAGN occurs in the liver, patients with hepatic impairment may have

reduced conversion capability and higher plasma PAA and PAA to PAGN ratio *[see Clinical Pharmacology (12.3)]*. Therefore, dosage for patients with moderate to severe hepatic impairment should be started at the lower end of the recommended dosing range and should be kept on the lowest dose necessary to control their ammonia levels *[see Dosage and Administration (2.5)]*.

10 OVERDOSAGE

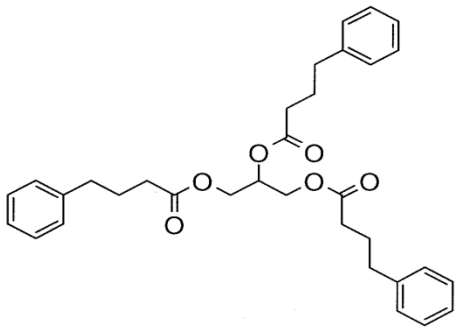
While there is no experience with overdosage in human clinical trials, PAA, a toxic metabolite of RAVICTI, can accumulate in patients who receive an overdose *[see Warnings and Precautions (5.1)]*.

If over-exposure occurs, call your Poison Control Center at 1-800-222-1222 for current information on the management of poisoning or overdosage.

11 DESCRIPTION

RAVICTI (glycerol phenylbutyrate) is a clear, colorless to pale yellow oral liquid. It is insoluble in water and most organic solvents, and it is soluble in dimethylsulfoxide (DMSO) and greater than 65% acetonitrile.

Glycerol phenylbutyrate is a nitrogen-binding agent. It is a triglyceride containing 3 molecules of PBA linked to a glycerol backbone, the chemical name of which is benzenebutanoic acid, 1', 1' ' –(1,2,3-propanetriyl) ester with a molecular weight of 530.67. It has a molecular formula of $C_{33}H_{38}O_6$. The structural formula is:



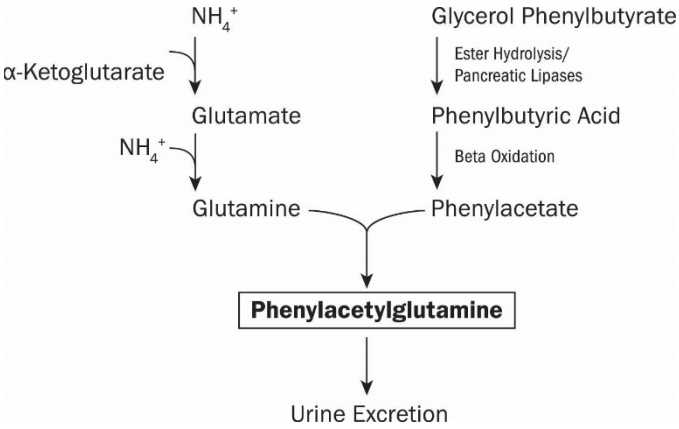
12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

UCDs are inherited deficiencies of enzymes or transporters necessary for the synthesis of urea from ammonia (NH_3, NH_4^+). Absence of these enzymes or transporters results in the accumulation of toxic levels of ammonia in the blood and brain of affected patients. RAVICTI is a triglyceride containing 3 molecules of PBA. PAA, the major metabolite of PBA, is the active moiety of RAVICTI. PAA conjugates with glutamine (which contains 2 molecules of nitrogen) via acetylation in the liver and kidneys to form PAGN, which is

excreted by the kidneys (Figure 1). On a molar basis, PAGN, like urea, contains 2 moles of nitrogen and provides an alternate vehicle for waste nitrogen excretion.

Figure 1: RAVICTI Mechanism of Action



12.2 Pharmacodynamics

Pharmacological Effects

In clinical studies, total 24-hour area under the plasma concentration-time curve (AUC) of ammonia levels was comparable at steady state during the switchover period between RAVICTI and sodium phenylbutyrate *[see Clinical Studies (14)]*.

Cardiac Electrophysiology

The effect of multiple doses of RAVICTI 13.2 g/day and 19.8 g/day (approximately 69% and 104% of the maximum recommended daily dosage) on QTc interval was evaluated in a randomized, placebo- and active-controlled (moxifloxacin 400 mg), four-treatment-arm, crossover study in 57 healthy subjects. The upper bound of the one-sided 95% CI for the largest placebo-adjusted, baseline-corrected QTc, based on individual correction method (QTcI) for RAVICTI, was below 10 ms.

12.3 Pharmacokinetics

Absorption

RAVICTI is a pro-drug of PBA. Upon oral ingestion, PBA is released from the glycerol backbone in the gastrointestinal tract by lipases. PBA derived from RAVICTI is further converted by β-oxidation to PAA.

In healthy, fasting adult subjects receiving a single oral dose of 2.9 mL/m^2 of RAVICTI, peak plasma levels of PBA, PAA, and PAGN occurred at 2 hours, 4 hours, and 4 hours, respectively. Upon single-dose administration of RAVICTI, plasma concentrations of PBA were quantifiable in 15 of 22 participants at the first sample time postdose (0.25 hours).

Mean maximum concentration (C_{max}) for PBA, PAA, and PAGN was 37.0 micrograms/mL, 14.9 micrograms/mL, and 30.2 micrograms/mL, respectively. In healthy subjects, intact glycerol phenylbutyrate was detected in plasma. While the study was inconclusive, the incomplete hydrolysis of glycerol phenylbutyrate cannot be ruled out.

In healthy subjects, the systemic exposure to PAA, PBA, and PAGN increased in a dose-dependent manner. Following 4 mL of RAVICTI 3 times a day for 3 days, the mean C_{max} and AUC were 66 micrograms/mL and 930 micrograms•h/mL for PBA and 28 micrograms/mL and 942 micrograms•h/mL for PAA, respectively. In the same study, following 6 mL of RAVICTI three times a day for 3 days, mean C_{max} and AUC were 100 micrograms/mL and 1400 micrograms•h/mL for PBA and 65 µg/mL and 2064 micrograms•h/mL for PAA, respectively.

In adult patients with UCDs receiving multiple doses of RAVICTI, maximum plasma concentrations at steady state ($C_{max,ss}$) of PBA, PAA, and PAGN occurred at 8 hours, 12 hours, and 10 hours, respectively, after the first dose in the day. Intact glycerol phenylbutyrate was not detectable in plasma in patients with UCDs.

In clinical studies of RAVICTI in patients with UCDs, the peak observed PAA concentrations by age group are shown in Table 2.

Table 2: Peak PAA Concentrations in Patients with UCDs Treated with RAVICTI in Clinical Trials

Age Range	RAVICTI Dose	Mean Peak PAA Concentration* (SD)	Median Peak PAA Concentration * (Range)
Less than 2 months (n=16)	3.1 to 12.7 mL/m^2/day (3.4 to 14 g/m^2/day)	257 (162)	205 (96 to 707)
2 months to less than 2 years (n=17)	3.3 to 12.3 mL/m^2/day (3.7 to 13.5 g/m^2/day)	142 (299)	35 (1 to 1215)
2 years to 17 years (n=53)	1.4 to 13.7 mL/m^2/day (1.5 to 15.1 g/m^2/day)	70 (79)	50 (1 to 410)
Adults (n=43)	0.6 to 14 mL/m^2/day (0.7 to 15.4 g/m^2/day)	39 (40)	25 (1.6 to 178)

*micrograms/mL

Distribution

In vitro, the extent of plasma protein binding for ^{14}C-labeled metabolites was 81% to 98% for PBA (over 1 to 250 micrograms/mL), and 37% to 66% for PAA (over 5 to 500 micrograms/mL). The protein binding for PAGN was 7% to 12% and no concentration effects were noted.

Elimination

Metabolism

Upon oral administration, pancreatic lipases hydrolyze RAVICTI (i.e., glycerol phenylbutyrate), and release PBA. PBA undergoes β-oxidation to PAA, which is conjugated

with glutamine in the liver and in the kidney through the enzyme phenylacetyl-CoA: L-glutamine-N-acetyltransferase to form PAGN. PAGN is subsequently eliminated in the urine.

Saturation of conjugation of PAA and glutamine to form PAGN was suggested by increases in the ratio of plasma PAA to PAGN with increasing dose and with increasing severity of hepatic impairment.

In healthy subjects, after administration of 4 mL, 6 mL, and 9 mL 3 times daily for 3 days, the ratio of mean $AUC_{0\text{-}23h}$ of PAA to PAGN was 1, 1.25, and 1.6, respectively. In a separate study, in patients with hepatic impairment (Child-Pugh B and C), the ratios of mean C_{max} values for PAA to PAGN among all patients dosed with 6 mL and 9 mL twice daily were 3 and 3.7.

In *in vitro* studies, the specific activity of lipases for glycerol phenylbutyrate was in the following decreasing order: pancreatic triglyceride lipase, carboxyl ester lipase, and pancreatic lipase–related protein 2. Further, glycerol phenylbutyrate was hydrolyzed *in vitro* by esterases in human plasma. In these *in vitro* studies, a complete disappearance of glycerol phenylbutyrate did not produce molar equivalent PBA, suggesting the formation of mono- or bis-ester metabolites. However, the formation of mono- or bis-esters was not studied in humans.

Excretion

The mean (SD) percentage of administered PBA excreted as PAGN was approximately 69% (17) in adults and 66% (24) in pediatric patients with UCDs at steady state. PAA and PBA represented minor urinary metabolites, each accounting for less than 1% of the administered dose of PBA.

Specific Populations

Age: Pediatric Population

Population pharmacokinetic modeling and dosing simulations suggest body surface area to be the most significant covariate explaining the variability of PAA clearance. PAA clearance was 10.9 L/h, 16.4 L/h, and 24.4 L/h, respectively, for patients ages 3 to 5, 6 to 11, and 12 to 17 years with UCDs.

In pediatric patients with UCDs (n = 14) ages 2 months to less than 2 years, PAA clearance was 6.8 L/h.

In pediatric patients with UCDs (n = 16) ages less than 2 months, PAA clearance was 3.8 L/h. The mean peak ratio of PAA to PAGN in UCD patients aged birth to less than 2 months was higher (mean: 1.6; range 0.1 to 7.1) than that of UCD patients aged 2 months to less than 2 years (mean 0.5; range 0.1 to 1.2).

Sex

In healthy adult subjects, a gender effect was found for all metabolites, with women generally having higher plasma concentrations of all metabolites than men at a given dose level. In healthy female subjects, mean C_{max} for PAA was 51 and 120% higher than in male volunteers after administration of 4 mL and 6 mL 3 times daily for 3 days, respectively. The dose normalized mean $AUC_{0\text{-}23h}$ for PAA was 108% higher in females than in males.

Renal Impairment

The pharmacokinetics of RAVICTI in patients with impaired renal function, including those with end-stage renal disease (ESRD) or those on hemodialysis, have not been studied *[see Use in Specific Populations (8.6)]*.

Hepatic Impairment

The effects of hepatic impairment on the pharmacokinetics of RAVICTI were studied in patients with mild, moderate and severe hepatic impairment of (Child-Pugh class A, B, and C, respectively) receiving 100 mg/kg of RAVICTI twice daily for 7 days.

Plasma glycerol phenylbutyrate was not measured in patients with hepatic impairment.

After multiple doses of RAVICTI in patients with hepatic impairment of Child-Pugh A, B, and C, geometric mean AUC_t of PBA was 42%, 84%, and 50% higher, respectively, while geometric mean AUC_t of PAA was 22%, 53%, and 94% higher, respectively, than in healthy subjects.

In patients with hepatic impairment of Child-Pugh A, B, and C, geometric mean AUC_t of PAGN was 42%, 27%, and 22% lower, respectively, than that in healthy subjects.

The proportion of PBA excreted as PAGN in the urine in Child-Pugh A, B, and C was 80%, 58%, and 85%, respectively, and, in healthy volunteers, was 67%.

In another study in patients with moderate and severe hepatic impairment (Child-Pugh B and C), mean C_{max} of PAA was 144 micrograms/mL (range: 14 to 358 micrograms/mL) after daily dosing of 6 mL of RAVICTI twice daily, while mean C_{max} of PAA was 292 micrograms/mL (range: 57 to 655 micrograms/mL) after daily dosing of 9 mL of RAVICTI twice daily. The ratio of mean C_{max} values for PAA to PAGN among all patients dosed with 6 mL and 9 mL twice daily were 3 and 3.7, respectively.

After multiple doses, a PAA concentration greater than 200 micrograms/mL was associated with a ratio of plasma PAA to PAGN concentrations higher than 2.5 *[see Dosage and Administration (2.5)]*.

Drug Interaction Studies

In vitro PBA or PAA did not induce CYP1A2, suggesting that *in vivo* drug interactions via induction of CYP1A2 is unlikely.

In *in vitro* studies, PBA at a concentration of 800 micrograms/mL caused greater than 60% reversible inhibition of cytochrome P450 isoenzymes CYP2C9, CYP2D6, and CYP3A4/5 (testosterone 6β-hydroxylase activity). The *in vitro* study suggested that *in vivo* drug interactions with substrates of CYP2D6 cannot be ruled out. The inhibition of CYP isoenzymes 1A2, 2C8, 2C19, and 2D6 by PAA at the concentration of 2.8 mg/mL was observed *in vitro*. Clinical implication of these results is unknown.

Effects of RAVICTI on other drugs

Midazolam

In healthy subjects, when oral midazolam was administered after multiple doses of RAVICTI (4 mL three times a day for 3 days) under fed conditions, the mean C_{max} and AUC for

midazolam were 25% and 32% lower, respectively, compared to administration of midazolam alone. In addition, the mean C_{max} and AUC for 1-hydroxy midazolam were 28% and 58% higher, respectively, compared to administration of midazolam alone *[see Drug Interactions (7.3)]*.

Celecoxib

Concomitant administration of RAVICTI did not significantly affect the pharmacokinetics of celecoxib, a substrate of CYP2C9. When 200 mg of celecoxib was orally administered with RAVICTI after multiple doses of RAVICTI (4 mL three times a day for 6 days) under fed conditions (a standard breakfast was consumed 5 minutes after celecoxib administration), the mean C_{max} and AUC for celecoxib were 13% and 8% lower than after administration of celecoxib alone.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In a 2-year study in Sprague-Dawley rats, glycerol phenylbutyrate caused a statistically significant increase in the incidence of pancreatic acinar cell adenoma, carcinoma, and combined adenoma or carcinoma at a dose of 650 mg/kg/day in males (4.7 times the dose of 6.9 mL/m^2/day in adult patients, based on combined AUCs for PBA and PAA) and 900 mg/kg/day in females (8.4 times the dose of 6.9 mL/m^2/day in adult patients, based on combined AUCs for PBA and PAA). The incidence of the following tumors was also increased in female rats at a dose of 900 mg/kg/day: thyroid follicular cell adenoma, carcinoma and combined adenoma or carcinoma, adrenal cortical combined adenoma or carcinoma, uterine endometrial stromal polyp, and combined polyp or sarcoma. The dose of 650 mg/kg/day in male rats is 3 times the dose of 7.5 mL/m^2/day in pediatric patients, based on combined AUCs for PBA and PAA. The dose of 900 mg/kg/day in female rats is 5.5 times the dose of 7.5 mL/m^2/day in pediatric patients, based on combined AUCs for PBA and PAA. In a 26-week study in transgenic (Tg.rasH2) mice, glycerol phenylbutyrate was not tumorigenic at doses up to 1000 mg/kg/day.

Mutagenesis

Glycerol phenylbutyrate was not genotoxic in the Ames test, the *in vitro* chromosomal aberration test in human peripheral blood lymphocytes, or the *in vivo* rat micronucleus test. The metabolites PBA, PAA, PAGN, and phenylacetylglycine were not genotoxic in the Ames test or *in vitro* chromosome aberration test in Chinese hamster ovary cells.

Impairment of Fertility

Glycerol phenylbutyrate had no effect on fertility or reproductive function in male and female rats at oral doses up to 900 mg/kg/day. At doses of 1200 mg/kg/day (approximately 7 times the dose of 6.9 mL/m^2/day in adult patients, based on combined AUCs for PBA and PAA), maternal toxicity was observed and the number of nonviable embryos was increased.

14 CLINICAL STUDIES

14.1 Clinical Studies in Adult Patients with UCDs

Active-Controlled, 4-Week, Noninferiority Study (Study 1)

A randomized, double-blind, active-controlled, crossover, noninferiority study (Study 1) compared RAVICTI to sodium phenylbutyrate by evaluating ammonia levels in patients with UCDs who had been on sodium phenylbutyrate prior to enrollment for control of their UCD. Patients were required to have a confirmed diagnosis of UCD involving deficiencies of CPS, OTC, or ASS, confirmed via enzymatic, biochemical, or genetic testing. Patients had to have no clinical evidence of hyperammonemia at enrollment and were not allowed to receive drugs known to increase ammonia levels (e.g., valproate), increase protein catabolism (e.g., corticosteroids), or significantly affect renal clearance (e.g., probenecid).

The primary endpoint was the 24-hour AUC (a measure of exposure to ammonia over 24 hours) for venous ammonia on days 14 and 28 when the drugs were expected to be at steady state. Statistical noninferiority would be established if the upper limit of the 2-sided 95% CI for the ratio of the geometric means (RAVICTI/sodium phenylbutyrate) for the endpoint was 1.25 or less.

Forty-five patients were randomized 1:1 to 1 of 2 treatment arms to receive either

- Sodium phenylbutyrate for 2 weeks → RAVICTI for 2 weeks; or
- RAVICTI for 2 weeks → sodium phenylbutyrate for 2 weeks.

Sodium phenylbutyrate or RAVICTI were administered three times daily with meals. The dose of RAVICTI was calculated to deliver the same amount of PBA as the sodium phenylbutyrate dose the patients were taking when they entered the study. Forty-four patients received at least 1 dose of RAVICTI in the study.

Patients adhered to a low-protein diet and received amino acid supplements throughout the study. After 2 weeks of dosing, by which time patients had reached steady state on each treatment, all patients had 24 hours of ammonia measurements.

Demographic characteristics of the 45 patients enrolled in Study 1 were as follows: mean age at enrollment was 33 years (range: 18 to 75 years); 69% were female; 33% had adult-onset disease; 89% had OTC deficiency; 7% had ASS deficiency; 4% had CPS deficiency.

RAVICTI was non-inferior to sodium phenylbutyrate with respect to the 24-hour AUC for ammonia. Forty-four patients were evaluated in this analysis. Mean 24-hour AUCs for ammonia during steady-state dosing were 866 micromol•h/L and 977 micromol•h/L with RAVICTI and sodium phenylbutyrate, respectively. The ratio of geometric means was 0.91 [95% CI 0.8, 1.04].

The mean ammonia levels over 24-hours after 2 weeks of dosing (on day 14 and 28) in the double-blind short-term study (Study 1) are displayed in Figure 2 below. The mean and median maximum ammonia levels (C_{max}) over 24 hours and 24-hour AUC for ammonia are summarized in Table 3. Ammonia values across different laboratories were normalized to a common normal range of 9 to 35 micromol/L using the following formula after standardization of the units to micromol/L:

Normalized ammonia (micromol/L) = ammonia readout in micromol/L x (35/ULN of a laboratory reference range specified for each assay)

Figure 2: Ammonia Levels in Adult Patients with UCDs in Short-Term Treatment Study 1

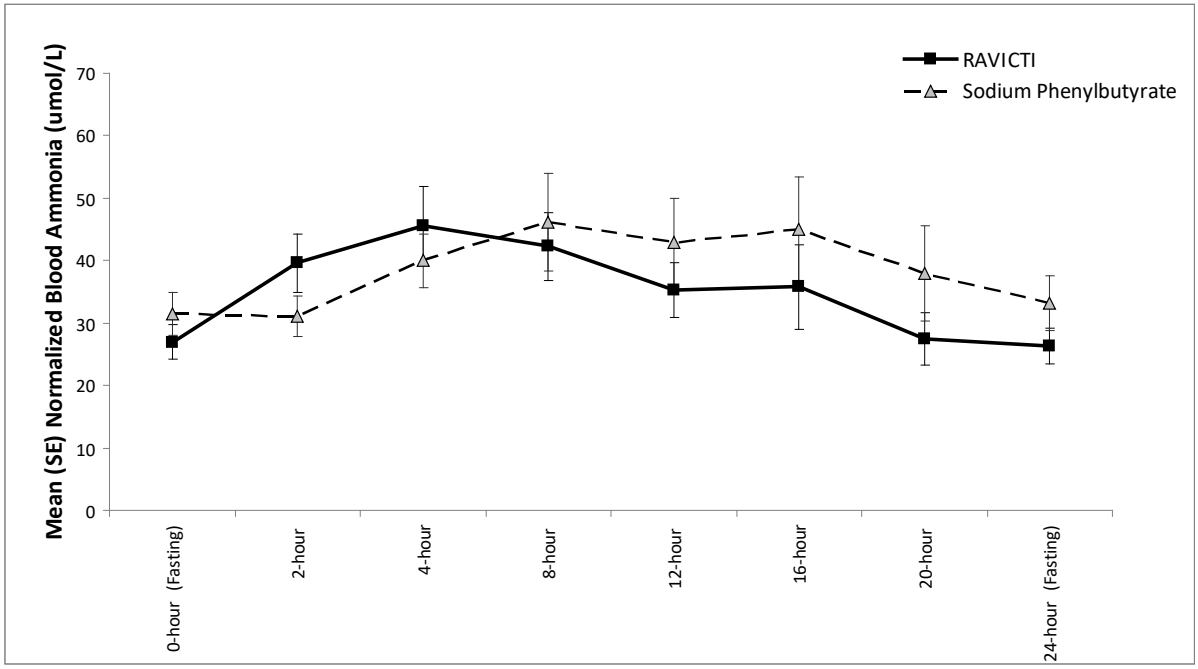


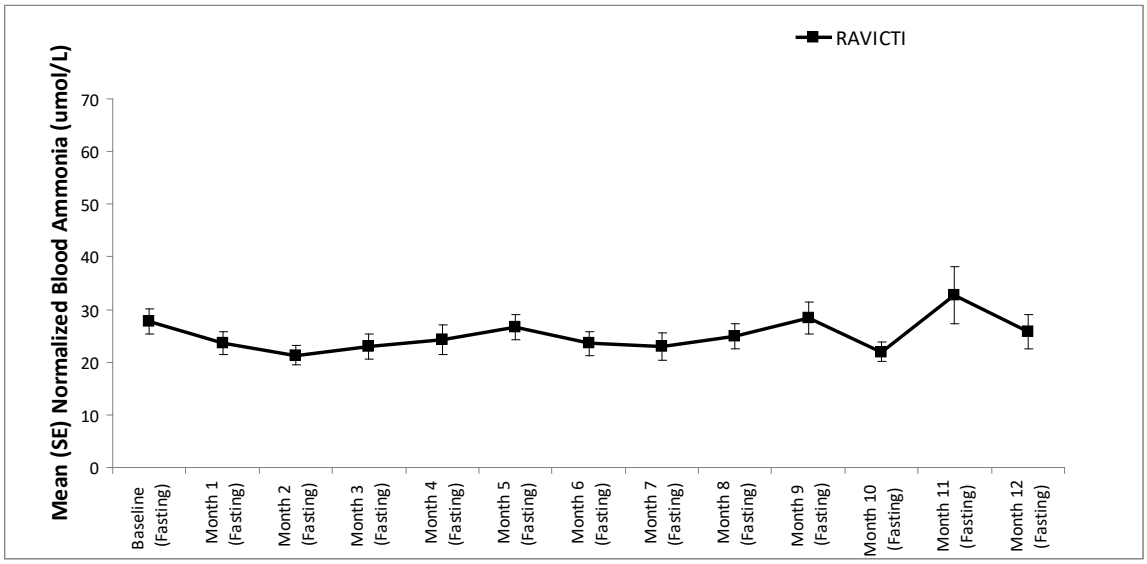
Table 3: Ammonia Levels in Adult Patients with UCDs in Short-Term Treatment Study 1

Timepoint	Ammonia (n=44)	
	Mean (SD)	**Median (min, max)**
Daily C_{max} (micromol/L)		
RAVICTI	61 (46)	51 (12, 245)
Sodium phenylbutyrate	71 (67)	46 (14, 303)
24-Hour AUC (micromol•h/L)		
RAVICTI	866 (661)	673 (206, 3351)
Sodium phenylbutyrate	977 (865)	653 (302, 4666)

Open-Label, Uncontrolled, Extension Study in Adults

A long-term (12-month), uncontrolled, open-label study (Study 2) was conducted to assess monthly ammonia control and hyperammonemic crisis over a 12-month period. A total of 51 adults were in the study and all but 6 had been converted from sodium phenylbutyrate to RAVICTI. Venous ammonia levels were monitored monthly. Mean fasting ammonia values in adults in Study 2 were within normal limits during long-term treatment with RAVICTI (range: 6 to 30 micromol/L). Of 51 adult patients participating in the 12-month, open-label treatment with RAVICTI, 7 patients (14%) reported a total of 10 hyperammonemic crises. The fasting ammonia measured during Study 2 is displayed in Figure 3. Ammonia values across different laboratories were normalized to a common normal range of 9 to 35 micromol/L.

Figure 3: Ammonia Levels in Adult Patients with UCDs in Long-Term Treatment Study 2



Open-Label, Long-Term Study in Adults

An open-label long-term, study (Study 5) was conducted to assess ammonia control in adult patients with UCDs. The study enrolled patients with UCDs who had completed the safety extensions of Study 1, Study 3 or Study 4 (Study 2, 3E and 4E, respectively). A total of 43 adult patients between the ages of 19 and 61 years were in the study. The median length of study participation was 1.9 years (range 0 to 4.5 years). Venous ammonia levels were monitored at a minimum of every 6 months. Mean fasting ammonia values in adult patients in Study 5 were within normal limits during long-term (24 months) treatment with RAVICTI (range: 24.2 to 31.4 micromol/L). Of the 43 adult patients participating in the open-label treatment with RAVICTI, 9 patients (21%) reported a total of 21 hyperammonemic crises. Ammonia values across different laboratories were normalized to a common normal range of 10 to 35 micromol/L.

14.2 Clinical Studies in Pediatric Patients 2 Years to 17 Years of Age with UCDs

The efficacy of RAVICTI in pediatric patients 2 years to 17 years of age with UCDs was evaluated in 2 fixed-sequence, open-label, sodium phenylbutyrate to RAVICTI switchover studies (Studies 3 and 4). Study 3 was 7 days in duration and Study 4 was 10 days in duration.

These studies compared ammonia levels of patients on RAVICTI to ammonia levels of patients on sodium phenylbutyrate in 26 pediatric patients between 2 months and 17 years of age with UCDs. Four patients less than 2 years of age were excluded from this analysis due to insufficient data. The dose of RAVICTI was calculated to deliver the same amount of PBA as the dose of sodium phenylbutyrate that patients were taking when they entered the trial. Sodium phenylbutyrate or RAVICTI were administered in divided doses with meals. Patients adhered to a low-protein diet throughout the study. After a dosing period with each treatment,

all patients underwent 24 hours of venous ammonia measurements, as well as blood and urine pharmacokinetic assessments.

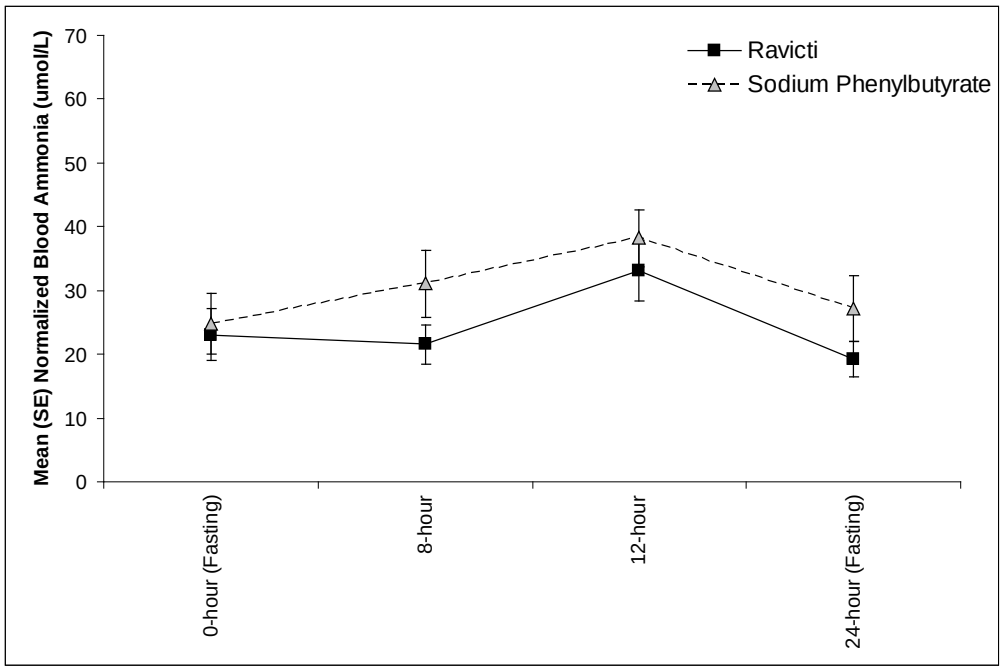
UCD subtypes included OTC (n=12), ASL (n=8), and ASS deficiency (n=2), and patients received a mean RAVICTI dose of 8 mL/m^2/day (8.8 g/m^2/day), with doses ranging from 1.4 to 13.1 mL/m^2/day (1.5 to 14.4 g/m^2/day). Doses in these patients were based on previous dosing of sodium phenylbutyrate.

The 24-hour AUCs for ammonia ($AUC_{0\text{-}24h}$) in 11 pediatric patients 6 years to 17 years of age with UCDs (Study 3) and 11 pediatric patients 2 years to 5 years of age with UCDs (Study 4) were similar between treatments. In pediatric patients 6 years to 17 years of age, the ammonia $AUC_{0\text{-}24h}$ was 604 micromol•h/L vs 815 micromol•h/L on RAVICTI vs sodium phenylbutyrate, respectively. In patients between 2 years and 5 years of age with UCDs, the ammonia $AUC_{0\text{-}24h}$ was 632 micromol•h/L vs 720 micromol•h/L on RAVICTI versus sodium phenylbutyrate, respectively.

The mean ammonia levels over 24 hours in open-label, short-term Studies 3 and 4 at common time points are displayed in Figure 4. Ammonia values across different laboratories were normalized to a common normal range of 9 to 35 micromol/L using the following formula after standardization of the units to micromol/L:

Normalized ammonia (micromol/L) = ammonia readout in micromol/L x (35/ULN of a laboratory reference range specified for each assay)

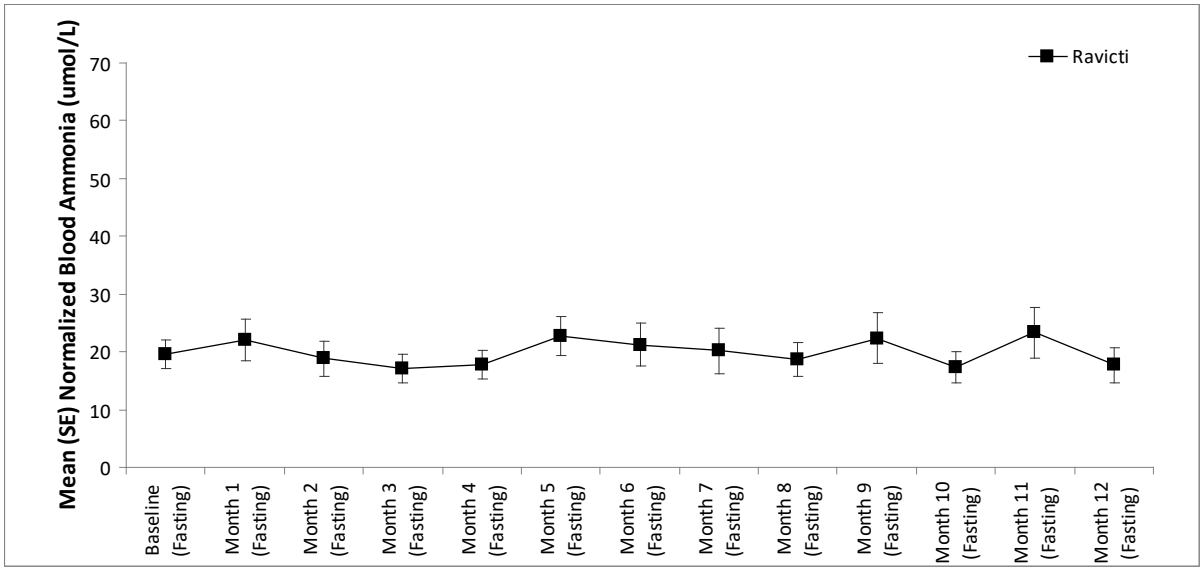
Figure 4: Ammonia Levels in Pediatric Patients 2 Years to 17 Years of Age with UCDs in Short-Term Treatment Studies 3 and 4



Open-Label, Uncontrolled, Extension Studies in Pediatric Patients 2 Years to 17 Years of Age

Long-term (12-month), uncontrolled, open-label studies were conducted to assess monthly ammonia control and hyperammonemic crises over a 12-month period. In two studies (Study 2, which also enrolled adults, and an extension of Study 3, referred to here as Study 3E), a total of 26 pediatric patients ages 6 years to 17 years were enrolled and all but 1 had been converted from sodium phenylbutyrate to RAVICTI. Mean fasting venous ammonia levels were within normal limits (range 17 to 23 micromol/L) during long-term treatment with RAVICTI. Of the 26 pediatric patients 6 years to 17 years of age participating in these two trials, 5 patients (19%) reported a total of 5 hyperammonemic crises. The fasting ammonia levels measured during these two extension studies in patients 6 years to 17 years are displayed in Figure 5. Ammonia values across different laboratories were normalized to a common normal range of 9 to 35 micromol/L.

Figure 5: Ammonia Levels in Pediatric Patients 2 Years to 17 Years of Age with UCDs in Long-Term Treatment Studies 2 and 3E



In an extension of Study 4 (referred to as Study 4E), after a median time on study of 4.5 months (range: 1 to 5.7 months), 2 of 16 pediatric patients ages 2 years to 5 years had experienced three hyperammonemic crises.

Open-Label, Long-Term Study in Pediatric Patients 1 Year to 17 Years of Age

An open-label, long-term study (Study 5) was conducted to assess ammonia levels in pediatric patients with UCD. The study enrolled patients with UCDs who had completed Studies 2, 3E and 4E. A total of 45 pediatric patients ages 1 year to 17 years were included in the study. The median length of treatment was 1.7 years (range 0.2 to 4.6 years). Venous ammonia levels were monitored at a minimum every 6 months. Mean ammonia values in pediatric patients in Study 5 were within normal limits during long-term (24 months) treatment with RAVICTI (range: 15.4 to 25.1 micromol/L). Of the 45 pediatric patients participating in the open-label treatment with RAVICTI, 11 patients (24%) reported a total of

22 hyperammonemic crises. Ammonia values across different laboratories were normalized to a common normal range of 10 to 35 micromol/L.

14.3 Clinical Studies in Pediatric Patients Less Than 2 Years of Age with UCDs

The efficacy of RAVICTI in pediatric patients less than 2 years of age with UCDs was evaluated in uncontrolled, open label studies (Studies 4/4E, 5 *[see Clinical Studies (14.2)]* and 6). A total of 17 pediatric patients with UCDs aged 2 months to less than 2 years participated in Studies 4/4E, 5 and 6. Study 6 enrolled 16 pediatric patients less than 2 months of age.

Uncontrolled, Open-Label Studies in Pediatric Patients Aged 2 Months to Less than 2 Years of Age (Studies 4/4E, 5)

A total of 7 patients with UCDs aged 2 months to less than 2 years participated in Studies 4/4E and 5. In these studies, there were 7, 6, 6, 6 and 3 pediatric patients who completed 1, 6, 9, 12 and 18 months, respectively (mean and median exposure of 15 and 17 months, respectively). Patients were converted from sodium phenylbutyrate to RAVICTI. The dosage of RAVICTI was calculated to deliver the same amount of PBA as the sodium phenylbutyrate dosage the patients were taking when they entered the study.

Patients received a mean RAVICTI dose of 7.5 mL/m^2/day (8.2 g/m^2/day), with doses ranging from 3.3 to 12.3 mL/m^2/day (3.7 to 13.5 g/m^2/day). Patients were dosed three times per day (n=3) or four times per day (n = 4).

Venous ammonia levels were monitored on days 1, 3, and 10 in Study 4 and at week 1 in Study 4E. Two patients had elevated ammonia values on day 1 of treatment (122 micromol/L and 111 micromol/L respectively) and neither had associated signs and symptoms of hyperammonemia. At day 10/week 1, six of the 7 patients had normal ammonia levels (less than 100 micromol/L) while the remaining patient had an elevated ammonia value on day 10 (168 micromol/L) and was asymptomatic.

During the extension period, venous ammonia levels were monitored monthly. Ammonia values across different laboratories were normalized (transformed) to a common normal pediatric range of 28 to 57 micromol/L for comparability. The mean ammonia levels in pediatric patients at month 1, 3, 6, 9 and 12 were 58, 49, 34, 65, and 31 micromol/L during treatment with RAVICTI, respectively.

Three patients reported a total of 3 hyperammonemic crises defined as having signs and symptoms consistent with hyperammonemia (such as frequent vomiting, nausea, headache, lethargy, irritability, combativeness, and/or somnolence) associated with high ammonia levels (greater than 100 micromol/L) and requiring medical intervention. Hyperammonemic crises were precipitated by gastroenteritis, vomiting, infection or no precipitating event (one patient). There were 4 patients who had one ammonia level that exceeded 100 micromol/L which was not associated with a hyperammonemic crisis.

Uncontrolled, Open-Label Study in Pediatric Patients Less Than 2 Years of Age (Study 6)

Study 6 was an uncontrolled, open label study in pediatric patients less than 2 years of age. The primary efficacy endpoint was successful transition to RAVICTI within a period of 4

days followed by 3 days of observation for a total of 7 days, where successful transition was defined as no signs and symptoms of hyperammonemia and a venous ammonia level less than 100 micromol/L. Ammonia levels were monitored for up to 4 days during transition and on day 7.

Pediatric Patients 2 Months to Less than 2 Years of Age

A total of 10 pediatric patients with UCDs aged 2 months to less than 2 years participated in Study 6, of which 6 patients converted from sodium phenylbutyrate to RAVICTI and 1 patient converted from sodium phenyl butyrate and sodium benzoate. The dosage of RAVICTI was calculated to deliver the same amount of PBA as the sodium phenylbutyrate dosage the patients were taking when they entered the trial. Two patients were treatment-naïve and received RAVICTI dosage of 7.5 mL/m^2/day and 9.4 mL/m^2/day, respectively. One additional patient was gradually discontinued from intravenous sodium benzoate and sodium phenylacetate while RAVICTI was initiated. The dosage of RAVICTI after transition was 8.5 mL/m^2/day.

There were 9, 7, 7, 4, 1 and 4 pediatric patients who completed 1, 3, 6, 12, 18 and 24 months, respectively (mean and median exposure of 9 and 9 months, respectively).

Patients received a mean RAVICTI dose of 8 mL/m^2/day (8.8 g/m^2/day), with doses ranging from 4.8 to 11.5 mL/m^2/day (5.3 to 12.6 g/m^2/day). Patients were dosed three times a day (n=6), four times a day (n = 2), or five or more times a day (n=2).

Nine patients successfully transitioned as defined by the primary endpoint. One additional patient developed hyperammonemia on day 3 of dosing and experienced surgical complications (bowel perforation and peritonitis) following jejunal tube placement on day 4. This patient developed hyperammonemic crisis on day 6, and subsequently died of sepsis from peritonitis unrelated to drug. Although two patients had day 7 ammonia values of 150 micromol/L and 111 micromol/L respectively, neither had associated signs and symptoms of hyperammonemia.

During the extension phase, venous ammonia levels were monitored monthly. Ammonia values across different laboratories were normalized (transformed) to a common normal pediatric range of 28 to 57 micromol/L for comparability. The mean normalized ammonia levels in pediatric patients at months 1, 2, 3, 4, 5, 6, 9, 12, 15, 18 and 24 were 67, 53, 78, 93, 78, 67, 38, 38, 36, 48 and 53 micromol/L during treatment with RAVICTI, respectively. Three patients reported a total of 7 hyperammonemic crises as defined in Study 4/4E and 5. Hyperammonemic crises were precipitated by vomiting, upper respiratory tract infection, gastroenteritis, decreased caloric intake or had no identified precipitating event (3 events). There was one additional patient who had one ammonia level that exceeded 100 micromol/L which was not associated with a hyperammonemic crisis.

Pediatric Patients Less than 2 Months of Age

A total of 16 pediatric patients less than 2 months of age participated in Study 6. Median age at enrollment was 0.5 months (range: 0.1 to 2 months). Eight patients had OTC deficiency, 7 patients had ASS deficiency, and 1 patient had ASL deficiency. Ten of the 16 patients transitioned from sodium phenylbutyrate to RAVICTI within 3 days of treatment and their initial dosage of RAVICTI was calculated to deliver the same amount of phenylbutyrate as

the sodium phenylbutyrate dosage administered prior to RAVICTI dosing. Three of the 16 patients were treatment-naïve and started RAVICTI at dosages of 9, 9.4, and 9.6 mL/m^2/day. The remaining 3 of the 16 patients transitioned from intravenous sodium benzoate and sodium phenylacetate to RAVICTI within 3 days of treatment and their initial dosages of RAVICTI were 10.4, 10.9, and 10.9 mL/m^2/day.

Of the 16 patients, 16, 14, 12, 6, and 3 patients were treated for 1, 3, 6, 12, and 18 months, respectively.

After the initial 7-day transition period, patients received a mean RAVICTI dosage of 8 mL/m^2/day (8.8 g/m^2/day), with doses ranging from 3.1 to 12.7 mL/m^2/day (3.4 to 14 g/m^2/day). The frequency of dosing varied throughout the study. The majority of patients were dosed three times per day with feeding. No patients discontinued during the 7-day transition phase. Ammonia values across different laboratories were normalized (transformed) to a common normal pediatric range of 28 to 57 micromol/L for comparability.

During the safety extension phase (months 1-24), venous ammonia levels were monitored monthly for the first 6 months of treatment and every 3 months thereafter until the patients terminated or completed the study. During the safety extension phase, 1 patient discontinued from the study due to an adverse event (increased hepatic enzymes), 2 patients were withdrawn from the study by their parent/guardian, and 4 patients discontinued from the study early to undergo a liver transplant (protocol-defined discontinuation criterion). The normalized ammonia levels in pediatric patients with available values (which varied by month of treatment) in Study 6 in patients less than 2 months of age are shown in Table 4.

Table 4: Ammonia* Levels in Pediatric Patients Less than 2 Months of Age with UCDs in Study 6

Month	N (patients with available ammonia level)	Normalized Ammonia (micromol/L)**	
		Mean (SD)	Median (Min, Max)
1	15	71 (52)	60 (18, 227)
2	11	58 (40)	50 (16, 168)
3	14	53 (34)	46 (11, 122)
4	11	94 (106)	64 (35, 407)
5	10	52 (18)	57 (27, 86)
6	9	49 (24)	42 (22, 91)
9	8	56 (34)	45 (22, 122)
12	6	35 (17)	36 (11, 60)
15	4	52 (12)	52 (39, 67)
18	3	64 (14)	63 (50, 78)
24	9	63 (29)	72 (23, 106)

*normalized ammonia (micromol/L) = ammonia readout in micromol/L x (35/ULN of a laboratory reference range specified for each assay)
**normal range: 28 to 57 micromol/L.

Five patients (all less than 1 month of age) experienced a total of 7 hyperammonemic crises defined as in Study 4/4E and 5. Hyperammonemic crises were precipitated by upper respiratory tract infection (2 events), change in diet (1 event), or had no identified precipitating event (4 events).

16 HOW SUPPLIED/STORAGE AND HANDLING

RAVICTI® (glycerol phenylbutyrate) oral liquid 1.1 g/mL is supplied in multi-use, 25-mL glass bottles. The bottles are supplied in the following configurations:

- NDC 42067-250-25: Single 25-mL bottle per carton

Store at 20°-25°C (68°-77°F) with excursions permitted to 15°-30°C (59°-86°F). Discard bottle 28 days after opening.

This drug was imported from Canada without the authorization of Horizon Therapeutics, Inc. under the State of Florida Section 804 Importation Program.

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17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Neurotoxicity *[see Warnings and Precautions (5.1)].*

- Inform patients/caregivers that adverse reactions of RAVICTI are sometimes the same as symptoms of high blood ammonia. Neurological adverse reactions may also be associated with the major metabolite of RAVICTI, PAA, and may be reversible. Blood tests for PAA may be done to measure the amount of PAA in the blood. Instruct the patient/caregiver to contact the healthcare provider immediately if the patient experiences: nausea, vomiting, headache, fatigue, somnolence, lightheadedness, confusion, exacerbation of preexisting neuropathy, disorientation, impaired memory, dysgeusia, or hypoacusis.

Pregnancy

Report pregnancies to Horizon at 1-866-479-6742 *[see Use in Specific Populations (8.1)]*.

Lactation

Advise patients that breastfeeding is not recommended during treatment with RAVICTI *[see Use in Specific Populations (8.2)]*.

Administration

- Instruct patients to take RAVICTI with food or formula and to administer directly into the mouth via oral syringe.
- Instruct patients to use the RAVICTI bottle and oral syringe as follows:
  - Use a new reclosable bottle cap adapter with each new bottle that is opened.
  - Open the RAVICTI bottle and twist on the new reclosable bottle cap adapter.
  - Use a new and dry oral syringe to withdraw each prescribed dose of RAVICTI.

- Discard the oral syringe after each dose.
- Tightly close the tethered tab on the reclosable bottle cap adapter after each use.
- Do not rinse the reclosable bottle cap adapter.
- Discard bottle and any remaining contents 28 days after opening.
- If water or moisture enters the RAVICTI bottle, the contents will become cloudy in appearance. If the contents of the bottle appear cloudy at any time, do not use the remaining RAVICTI in the bottle and return it to the pharmacy to be discarded.

- Instruct that RAVICTI should be administered just prior to breastfeeding in infants who are breastfeeding.
- Instruct patients to take RAVICTI orally, even if they have a nasogastric and/or gastrostomy tube. For patients who cannot swallow and who have a nasogastric tube or gastrostomy tube in place, instruct patients/caregivers to administer RAVICTI as follows:
  - Utilize a new dry oral syringe to withdraw the prescribed dosage of RAVICTI from the bottle.
  - Place the tip of the syringe into the gastrostomy/nasogastric tube.
  - Utilizing the plunger of the syringe, administer RAVICTI into the tube.
  - Use a separate syringe to flush the nasogastric/gastrostomy tube. Flush once with 10 mL of water or formula and allow the flush to drain.
  - If needed, flush a second time with an additional 10 mL of water or formula to clear the tube.

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

RAV-US-PI-001

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 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.

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 all of your medical conditions, including 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. If you become pregnant during treatment with RAVICTI, call Horizon at 1-866-479-6742 to report the pregnancy.
- 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.
- In an infant who is breastfeeding, give RAVICTI just before breastfeeding.
- RAVICTI is an oral liquid that is taken by mouth using an oral syringe.
- Ask your pharmacist for oral syringes and a reclosable bottle cap adapter for each bottle you receive if you do not have them.
- Use the RAVICTI bottle and oral syringe as follows:
  - Use a new reclosable bottle cap adapter with each new RAVICTI bottle that is opened.
  - Open the RAVICTI bottle and twist on the new reclosable bottle cap adapter.
  - Use a new dry oral syringe to remove each prescribed dose of RAVICTI.
  - Throw away (discard) the oral syringe after each dose.
  - Tightly close the tethered tab on the reclosable bottle cap adapter after each use.
  - Do not rinse the reclosable bottle cap adapter.
  - If water or moisture enters the RAVICTI bottle, the contents will become cloudy in appearance. If the contents appear cloudy at any time, **do not** use the remaining RAVICTI and return the bottle to your pharmacy to throw it away.
  - Throw away the bottle and any unused RAVICTI 28 days after opening.
- 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 a new dry oral syringe to withdraw each 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.
- Use a separate syringe to flush the nasogastric or gastrostomy 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
- constipation
- diarrhea
- fever
- reduced food intake
- cough
- stuffy nose
- runny nose
- skin rash
- small round bumps on the skin

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

- vomiting
- rash
- gastroesophageal reflux
- increased levels of liver enzymes in the blood
- decreased appetite and reduced food intake
- low red blood cell count (anemia)
- cough
- loss of too much body fluid (dehydration)
- too much acid in the blood (acidosis)
- high blood platelet count (thrombocytosis)
- low blood platelet count (thrombocytopenia)
- low blood neutrophil count (type of white blood cell) (neutropenia)
- high blood white blood cell count (lymphocytosis)
- diarrhea
- gas
- constipation
- fever
- drowsiness (lethargy)
- irritability
- agitation

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 Therapeutics USA, Inc., Lake Forest, IL 60045.

For more information, go to www.RAVICTI.com or call 1-866-479-6742.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: September 2021

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Imported by: LifeScience Logistics, 310 N. Galloway Rd., Lakeland, FL 33815

Annotated Label Comparisons

PI Comparisons FDA VS. FLCPDIP
Differences
Updated information Adverse Reactions Contact
How Supplied/Storage and Handling added SIP804 language
Patient Information added SIP804 language
Listed new NDC #
Added Importation language & Importer name & address
Listed only drug strength purchased for program

FDA

ADVERSE REACTIONS

Most common adverse reactions (≥10%) in adults are: diarrhea, flatulence, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Horizon at 1-866-479-6742 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

16 HOW SUPPLIED/STORAGE AND HANDLING

RAVICTI® (glycerol phenylbutyrate) oral liquid 1.1 g/mL is supplied in multi-use, 25-mL glass bottles. The bottles are supplied in the following configurations:

- NDC 75987-050-06: Single 25-mL bottle per carton
- NDC 75987-050-07: Four 25-mL bottles per carton

Store at 20°-25°C (68°-77°F) with excursions permitted to 15°-30°C (59°-86°F). Discard bottle 28 days after opening.

What are the ingredients in RAVICTI?
Active ingredient: glycerol phenylbutyrate
Distributed by: Horizon Therapeutics USA, Inc., Deerfield, IL 60015.

For more information, go to www.RAVICTI.com or call 1-866-479-6742.
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FLSIP

ADVERSE REACTIONS

Most common adverse reactions (≥10%) in adults are: diarrhea, flatulence, and headache. (6.1)

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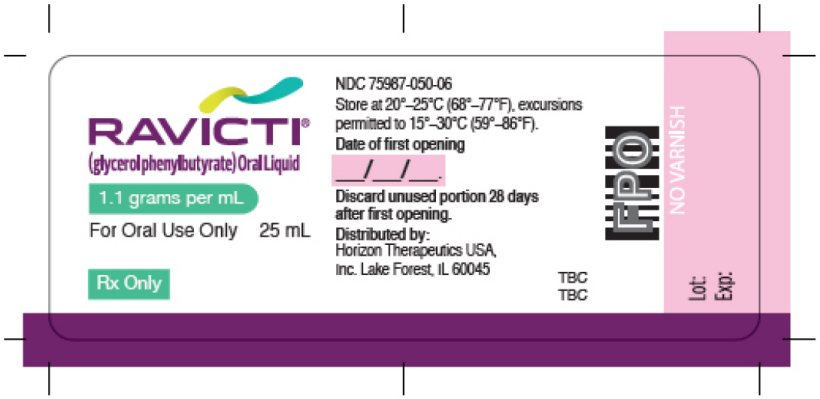
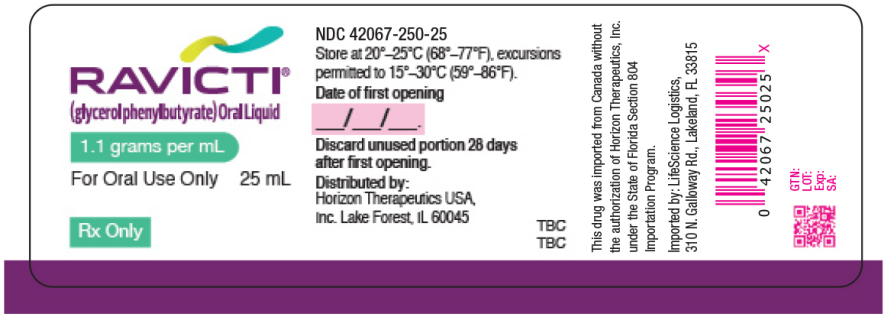
Proposed Package Label



Label Comparisons FDA VS. FLCPDIP
Differences
NDC
GTN
Bar Codes FPO with Associated NDCs
SIP804 Importation Language
Label SIZE due to production process & adding SIP804 language
Importer Name & Address
Brand logos FPO low resolution. Native art files requested upon SIP804 approval.



Comparisons
FDA to FLSIP

Recent FDA Approved Label	US Proprietary Name	US Generic Name	US Strength	NDC	NDA or ANDA	Applicant Holder Name	Applicant Holder Address	US Active Ingredients	Date Labeling Prepared for FLSIP	LSL Proprietary Name	LSL Generic Name	FLSIP Strength	LSL NDC	LSL Relabeler Name	Applicant Holder Name	Applicant Holder Address	FLSIP Active Ingredients
9/15/2021	RAVICTI	Glycerol phenylbutyrate	1.1 g/mL 25mL	75987-050-06	NDA203284	Horizon Therapeutics USA, Inc.,	Deerfield, IL 60015.	Glycerol phenylbutyrate	Aug-23	RAVICTI	Glycerol phenylbutyrate	1.1 g/mL 25mL	42067-250-25	LifeScience Logistics, LLC	Horizon Therapeutics USA, Inc.,	Deerfield, IL 60015.	Glycerol phenylbutyrate

Comparisons
Canada to FDA

Active Ingredient	Canadian Submission Number	Canadian Proprietary Name	Canadian Generic Name	DIN	Date Labeling Approved	Company Name	Address	Canadian Strength	Dosage Form	# of active Ingred.	Canadian Active Ingredients	US Proprietary Name	US Generic Name	US Strength	NDC	NDA or ANDA	Applicant Holder Name	US Active Ingredients
GLYCEROL PHENYLBUTYRATE	259175	RAVICTI	GLYCEROL PHENYLBUTYRATE	2453304	Revision: NOV 23, 2022	Horizon Therapeutics Ireland DAC	70 St. Stephen's Green Dublin 2, Ireland	1.1 g/mL 25mL	Oral Liquid	1	GLYCEROL PHENYLBUTYRATE	RAVICTI	Glycerol phenylbutyrate	1.1 g/mL 25mL	75987-050-06	NDA203284	Horizon Therapeutics	Glycerol phenylbutyrate

Carton Comparisons FDA Carton VS. FLCPDIP
Carton Differences
NDC
GTN
Bar Codes FPO with Associated NDCs
SIP804 Importation Language
Brand logos FPO low resolution. Native art files requested upon SIP804 approval.
Importer Name & Address

Canadian Monograph

PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr **RAVICTI®**

glycerol phenylbutyrate

Oral Liquid, 1.1 g/mL

Alimentary Tract and Metabolism Product

Horizon Therapeutics Ireland DAC
70 St. Stephen's Green
Dublin 2, Ireland

Date of Initial Authorization:
MAR 18, 2016

Date of Revision:
NOV 23, 2022

Submission Control Number: 259175

RECENT MAJOR LABEL CHANGES

1 INDICATIONS, 1.1 Pediatrics	11/2022
2 CONTRAINDICATIONS	11/2022
4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment	11/2022
4 DOSAGE AND ADMINISTRATION, 4.4 Administration	11/2022
7 WARNINGS AND PRECAUTIONS, 7.1.3 Pediatrics	11/2022

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

RAVICTI (glycerol phenylbutyrate) 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 should be used with dietary protein restriction and, in some cases, dietary supplements (e.g., essential amino acids, arginine, citrulline, and protein-free calorie supplements).

Limitations of Use:

RAVICTI is not indicated for treatment of acute hyperammonemia in patients with UCDs because more rapidly acting interventions are essential to reduce plasma ammonia levels.

Safety and efficacy for treatment of patients with *N*-acetylglutamate synthase (NAGS) deficiency have not been established.

1.1 Pediatrics

Pediatrics (<18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of RAVICTI in pediatric patients has been established. Therefore, Health Canada has authorized an indication for pediatric use (see 1 INDICATIONS).

1.2 Geriatrics

Geriatrics (>65 years of age): Clinical studies of RAVICTI did not include sufficient numbers of subjects ≥65 years of age to determine whether they respond differently than younger subjects (see 7 WARNINGS AND PRECAUTIONS, Special Populations).

2 CONTRAINDICATIONS

RAVICTI is contraindicated in patients who are:

- hypersensitive to RAVICTI or its metabolites (phenylbutyric acid [PBA], phenylacetic acid [PAA], and phenylacetylglutamine [PAGN]) or to any ingredient in the formulation, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING).
- breastfeeding.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

RAVICTI should be prescribed by a physician experienced in the management of UCDs.

RAVICTI must be combined with dietary protein restriction and, in some cases, dietary supplements (essential amino acids, carnitine supplementation, arginine, citrulline, and protein free calorie supplements).

The daily dose should be individually adjusted according to the patient's estimated urea synthetic capacity, if any, protein tolerance, and the daily dietary protein intake needed to promote growth and

development. 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 assuming all the waste nitrogen is covered by RAVICTI and excreted as PAGN.

4.2 Recommended Dose and Dosage Adjustment

Recommended Dose

The recommended total daily dose range of RAVICTI, based upon body surface area, is 4.5 mL/m^2/day to 11.2 mL/m^2/day (5.0 g/m^2/day to 12.4 g/m^2/day) and should take into account the following:

- Patients 2 years of age and older: The total daily dose should be divided into 3 equally divided dosages and given with each meal or feeding, each rounded up to the nearest 0.5 mL.
- Patients less than 2 years: The total daily dose should be divided into 3 or more equally divided dosages, each rounded up to the nearest 0.1 mL.

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.

The recommended starting dosages for patients switching from sodium phenylbutyrate to RAVICTI and patients naïve to PBA may be different. The total daily dosage should not exceed 17.5 mL.

Patients switching from sodium phenylbutyrate to RAVICTI should receive the dosage of RAVICTI that contains the same amount of PBA. 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

Dosage Adjustment

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) in patients 6 years and older. In infants and young children (generally below 6 years of age) where obtaining fasting ammonia is problematic due to frequent feedings, the first ammonia of the morning should be used. If available, the ratio of PAA to PAGN in the same plasma sample may provide additional information to assist in dosage adjustment decisions.

Adjustment Based on Urinary Phenylacetylglutamine (U-PAGN): 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 recommended 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-hour U-PAGN level and the estimated RAVICTI dose needed per gram of dietary protein ingested.

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 9 DRUG INTERACTIONS).

Adjustment Based on Plasma PAA and PAGN: If symptoms of vomiting, nausea, headache, somnolence, confusion, or sleepiness are present in the absence of high ammonia or intercurrent illness, measurement of plasma PAA levels may be useful to guide dosing (see 7 WARNINGS AND PRECAUTIONS). The ratio of PAA to PAGN in plasma, both measured in µg/mL, may provide additional information to assist in dose adjustment decisions. The PAA to PAGN ratio has been observed to be

generally less than 1 in patients without PAA accumulation. In patients with a PAA to PAGN ratio exceeding 2.5, 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. In such cases, dose reduction or increasing the dosing frequency may result in a lower plasma PAA level and PAA to PAGN ratio. Ammonia levels must be monitored closely when changing the dose of glycerol phenylbutyrate.

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 dosing range (4.5 mL/m^2/day) and the dosage should be kept at the lowest necessary to control the patient's plasma ammonia.

4.4 Administration

For oral administration.

RAVICTI should be taken with food or formula and administered directly into the mouth via oral syringe.

RAVICTI should be administered just prior to breastfeeding in infants who are breastfeeding.

Preparation for Nasogastric Tube or Gastrostomy Tube Administration

In vitro studies evaluating the percent recovery of total dose delivered with nasogastric or gastrostomy tubes demonstrated the percent of dose recovered was >99% for doses >1 mL and 70% for a 0.5 mL dose.

It is recommended that all patients who can swallow take RAVICTI orally, even those with nasogastric and/or gastric tubes. However, for patients who cannot swallow, a nasogastric tube or gastrostomy tube may be used to administer RAVICTI as follows:

- Utilize a new dry oral syringe to withdraw the prescribed dosage of RAVICTI from the bottle. Discard the oral syringe after each dose.
- Place the tip of the syringe into the tip of the gastrostomy/nasogastric tube.
- Utilizing the plunger of the syringe, administer RAVICTI into the tube.
- Use a separate syringe to flush the nasogastric/gastrostomy tube. Flush with at least 10 mL of water or formula and allow the flush to drain.
- If needed, flush a second time with an additional 10 mL of water or formula to clear the tube.

For 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. Therefore, these patients should be closely monitored using ammonia levels following initiation of RAVICTI dosing or dosage adjustments.

See 12 SPECIAL HANDLING INSTRUCTIONS.

4.5 Missed Dose

In the event a dose is missed, the dose should be taken as soon as the patient remembers. If it is close to the patient's next dose, skip the missed dose and continue with the next scheduled dose. The dose should not be doubled to make up for the missed dose.

5 OVERDOSAGE

While there is no experience with overdosage in human clinical trials, PAA, a toxic metabolite of RAVICTI, can accumulate in patients who receive an overdose (see 7 WARNINGS AND PRECAUTIONS).

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Oral	1.1 g/mL glycerol phenylbutyrate (delivers 1.02 g/mL of PBA)	There are no nonmedicinal ingredients

RAVICTI is a colourless to pale yellow oral liquid.

RAVICTI is supplied in multi-use, 25-mL glass bottles. The bottles are supplied in the following configuration:

- Single 25-mL bottle per carton

7 WARNINGS AND PRECAUTIONS

General

Acute hyperammonemic encephalopathy may occur in a number of patients even when they are on therapy.

RAVICTI is not recommended for the management of acute hyperammonemia, which is a medical emergency.

Cardiovascular

RAVICTI is associated with an increase in heart rate (see 10.2 Pharmacodynamics). Caution should be observed in patients who have conditions that could be worsened by an increase in heart rate such as tachyarrhythmias or ischemic heart disease.

Hepatic/Biliary/Pancreatic

Since the metabolism and excretion of RAVICTI involves the liver, RAVICTI should be used with caution in patients with hepatic insufficiency (see 10.3 Pharmacokinetics).

Pancreatic lipases may be necessary for intestinal hydrolysis of RAVICTI, allowing release of PBA and subsequent formation of PAA, the active moiety. It is not known whether pancreatic and extrapancreatic lipases are sufficient for hydrolysis of RAVICTI. If there is inadequate intestinal hydrolysis of RAVICTI, impaired absorption of PBA and hyperammonemia could occur.

Monitoring and Laboratory Tests

Adjustment may be based on monitoring of plasma ammonia, glutamine, U-PAGN, and/or plasma PAA and PAGN as well as the ratio of plasma PAA to PAGN (see 4.2 Recommended Dose and Dosage Adjustment).

Neurologic

The major metabolite of RAVICTI, PAA, is associated with signs and symptoms of 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 intravenous (IV) PAA. In this study, adverse events were reversible.

In controlled clinical trials in UCD patients who had been on sodium phenylbutyrate prior to administration of RAVICTI, mean (standard deviation or SD) maximum PAA concentrations after dosing with RAVICTI were 38.5 (102.6) µg/mL in adult patients and 87.3 (11.5) µg/mL in pediatric patients (N=26). No correlation between PAA levels and neurotoxicity symptoms was identified in UCD patients.

If symptoms of vomiting, nausea, headache, somnolence, confusion, or sleepiness are present in the absence of high ammonia or other intercurrent illnesses, measure plasma PAA and plasma PAA to PAGN and consider reduction of RAVICTI dosage if the PAA level exceeds 500 µg/mL or the PAA:PAGN ratio exceeds 2.5.

Renal

RAVICTI has not been studied in patients with impaired renal function. As RAVICTI excretion involves the kidneys, it should be used with caution in patients with renal insufficiency, including those with end-stage renal disease (ESRD) or those on hemodialysis.

7.1 Special Populations

7.1.1 Pregnant Women

Pregnant Women: There are no adequate and well controlled studies of RAVICTI in pregnant women. Studies in rats have shown reproductive toxicity (see 16 NON-CLINICAL TOXICOLOGY). RAVICTI should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

7.1.2 Breast-feeding

It is unknown if RAVICTI is excreted in human milk. It has not been determined if RAVICTI or its metabolites are secreted in human milk and therefore the use of RAVICTI is contraindicated during breastfeeding (see 2 CONTRAINDICATIONS).

7.1.3 Pediatrics

Clinical trials in pediatrics demonstrated that the PAA concentration is high in pediatrics compared to adults and inversely proportional to the age. The highest concentration was noted in pediatrics less than 2 months of age (see Table 5). The PAA to PAGN ratio less than 1 indicates that the PAA is not accumulated. If the ratio of PAA to PAGN ratio exceeds 2.5, a further increase in RAVICTI dose may not increase PAGN formation due to saturation of the conjugation reaction (see 4.2 Recommended Dose and Dosage Adjustment).

If symptoms of vomiting, nausea, headache, somnolence, confusion, or sleepiness are present in the

absence of high ammonia or intercurrent illness, measurement of plasma PAA levels and PAA to PAGN ratio may be useful to guide dosing (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, Neurologic). In such cases, a dose reduction or increasing the dosing frequency may result in a lower plasma PAA level and PAA to PAGN ratio. Ammonia levels must be monitored closely when changing the dose of glycerol phenylbutyrate.

7.1.4 Geriatrics

Geriatrics (>65 years of age): Clinical studies of RAVICTI did not include sufficient numbers of subjects ≥65 years of age to determine whether they respond differently than younger subjects. In general, dose selection for a newly diagnosed elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of concomitant disease, including decreased hepatic, renal, or cardiac function, or concomitant drug therapy.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The incidence of serious adverse events in long term clinical trials with RAVICTI was 26% and consisted primarily of hyperammonemia (18%).

The most common adverse drug reactions among all patients taking RAVICTI in clinical trials include diarrhea, flatulence, headache, decreased appetite, vomiting, nausea, fatigue, and skin odor.

Adverse drug reactions that resulted in clinical intervention in UCD patients who participated in clinical trials were mostly gastrointestinal reactions (flatulence, nausea, vomiting, abdominal distention) or neurological reactions (dysgeusia, lethargy, speech disorder, paresthesia, tremor).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials, therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Assessment of adverse drug reactions was based on exposure in 114 UCD patients (65 adults and 49 children between the ages of 2 months and 17 years) across four short term active control studies and three long term (12 month) uncontrolled clinical studies. Table 2 shows the adverse reactions reported in ≥2% of patients receiving RAVICTI.

Table 2: Adverse Reactions Reported in ≥2% of UCD Patients in Clinical Trials

System Organ Class Preferred Term	Number (%) of Patients in Pooled Studies	
	Short-Term Controlled Studies (N=80)	Long-Term Open-Label Studies (N=100)
Gastrointestinal disorders		
Abdominal distension	2 (2.5)	2 (2.0)
Abdominal pain	3 (3.8)	2 (2.0)
Abdominal pain upper	2 (2.5)	4 (4.0)
Constipation	1 (1.3)	2 (2.0)

System Organ Class Preferred Term	Number (%) of Patients in Pooled Studies	
	Short-Term Controlled Studies (N=80)	Long-Term Open-Label Studies (N=100)
Diarrhoea	7 (8.8)	4 (4.0)
Dyspepsia	2 (2.5)	3 (3.0)
Flatulence	7 (8.8)	3 (3.0)
Nausea	1 (1.3)	5 (5.0)
Oral discomfort	0	2 (2.0)
Retching	0	2 (2.0)
Vomiting	1 (1.3)	7 (7.0)
General disorders and administration site conditions		
Fatigue	3 (3.8)	4 (4.0)
Investigations		
Anion gap increased	0	2 (2.0)
Vitamin D decreased	0	2 (2.0)
Metabolism and nutrition disorders		
Decreased appetite	1 (1.3)	7 (7.0)
Increased appetite	3 (3.8)	2 (2.0)
Nervous system disorders		
Dizziness	0	3 (3.0)
Headache	7 (8.8)	3 (3.0)
Tremor	0	2 (2.0)
Psychiatric disorders		
Food aversion	0	2 (2.0)
Reproductive system and breast disorders		
Metrorrhagia	0	2 (2.0)
Skin and subcutaneous tissue disorders		
Acne	0	2 (2.0)
Skin odour abnormal	0	6 (6.0)

8.2.1 Clinical Trials Adverse Reactions – Pediatrics

Adverse reactions reported in at least 10% of pediatric patients ages 2 years to 17 years were upper abdominal pain, rash, nausea, vomiting, diarrhea, decreased appetite, and headache.

RAVICTI has been evaluated in 17 patients with UCDs ages 2 months to less than 2 years in 3 open-label studies. The median exposure was 6 months (range 0.2 to 20 months). Adverse reactions reported in at least 10% of pediatric patients aged 2 months to less than 2 years were neutropenia, vomiting, constipation, diarrhea, pyrexia, upper respiratory tract infection, gastroenteritis, otitis media, urinary tract infection, viral infection, hyperammonemia, hypophagia, cough, nasal congestion, rhinorrhea, rash, and papule.

RAVICTI has been evaluated in 16 patients with UCDs less than 2 months of age (age range 0.1 to 2 months, median age 0.5 months) in a single, open-label study. The median exposure was 10 months (range 2 to 20 months). Adverse reactions reported in at least 10% of pediatric patients aged less than 2 months were vomiting, dermatitis diaper, rash, gastroesophageal reflux, increased hepatic enzymes, feeding disorder (decreased appetite, hypophagia), anemia, cough, hyperammonemia, dehydration, metabolic acidosis, thrombocytosis, thrombocytopenia, neutropenia, lymphocytosis, diarrhea, flatulence, constipation, pyrexia, lethargy, irritability/agitation, upper respiratory infection, urinary tract infection, ear infection, nasopharyngitis, oral candidiasis, oropharyngeal pain, nasal congestion and respiratory syncytial virus infection.

8.3 Less Common Clinical Trial Adverse Reactions

The adverse reactions that occurred in <2% of UCD patients (65 adults and 49 children between the ages of 2 months and 17 years) across four short term active control studies and three long term (12 month) uncontrolled clinical studies include:

Gastrointestinal disorders: abdominal discomfort, abnormal faeces, defaecation urgency, dry mouth, eructation, gastrointestinal pain, painful defaecation, steatorrhoea, stomatitis
Musculoskeletal and connective tissue disorders: muscle spasms
Nervous system disorders: dysgeusia, lethargy, paraesthesia, somnolence
Psychiatric disorders: confusional state
Reproductive system and breast disorders: amenorrhoea, menstruation irregular
Respiratory, thoracic and mediastinal disorders: dysphonia, oropharyngeal pain, throat irritation
Vascular disorders: hot flush

8.3.1 Less Common Clinical Trial Adverse Reactions – Pediatrics

Less common (<10% of patients) clinical trial adverse reactions in pediatric patients ages 2 months to less than 2 years of age (n = 17) with UCD include:

Blood and lymphatic system disorders: anaemia

Gastrointestinal disorders: cheilitis, flatulence, gastroesophageal reflux disease, teething

General disorders and administration site conditions: decreased activity, infusion site extravasation, pneumatosis

Infections and infestations: conjunctivitis, croup infection, ear infection, gastroenteritis viral, hand-food-and-mouth disease, nasopharyngitis, oral candidiasis, periorbital cellulitis, pneumonia, rhinovirus infection

Injury, poisoning and procedural complications: chemical burn of skin, stoma site reaction, thermal burn, tibia fracture

Investigations: aspartate aminotransferase increased, blood bicarbonate decreased, breath sounds abnormal, international normalised ratio increased, prothrombin time prolonged

Metabolism and nutrition disorders: decreased appetite, feeding disorder, hypokalemia, metabolic acidosis

Nervous system disorders: ataxia, brain oedema, gross motor delay, hyporeflexia, hypotonia, lethargy, seizure, somnolence

Renal and urinary disorders: vesicoureteric reflux

Respiratory, thoracic and mediastinal disorders: rhinorrhea, apnoeic attack, dyspnoea, pharyngeal erythema, wheezing

Skin and subcutaneous disorders: dermatitis, nail ridging, rash papular

Vascular disorders: deep vein thrombosis

Less common (<10% of patients) clinical trial adverse reactions in pediatric patients less than 2 months of age (n = 16) with UCD include:

Blood and lymphatic system disorders: leukocytosis, lymphocytosis, microcytic anaemia

Cardiac disorders: tachycardia

Gastrointestinal disorders: dysphagia, post-tussive vomiting

General disorders and administration site conditions: catheter site rash, device occlusion, drug withdrawal syndrome, medical device site haemorrhage

Hepatobiliary disorders: hepatic calcification

Infections and infestations: angular cheilitis, bacteraemia, candida infection, cellulitis, croup infection, device related infection, gastroenteritis, gastrointestinal viral infection, lower respiratory tract infection, medical device site infection, meningitis bacterial, otitis media, otitis media acute, rhinovirus infection, sinusitis, tracheitis, viral infection

Injury, poisoning and procedural complications: arthropod bite, stoma site reaction

Investigations: alanine aminotransferase increased, amino acid level decreased, amino acid level increased, ammonia increased, anion gap increased, aspartate aminotransferase increased, blood bicarbonate decreased, blood urea decreased, body heigh below normal, carbon dioxide decreased, gamma-glutamyltransferase increased, platelet count increased transaminases increased, weight decreased

Metabolism and nutrition disorders: protein deficiency

Musculoskeletal and connective tissue disorders: torticollis

Nervous system disorders: tremor

Renal and urinary disorders: nephrolithiasis

Respiratory, thoracic, and mediastinal disorders: atelectasis, pneumothorax, tachypnoea, use of accessory respiratory muscles

Skin and subcutaneous tissue disorders: eczema, red man syndrome, seborrheic dermatitis

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Table 3: Abnormal Hematologic and Clinical Chemistry Findings

Lab Test (Unit)	Patients with clinically significant abnormalities N (%)	Total Number of Clinically Significant Abnormalities	Mean (SD) of lab value	Mean Change (SD) from Lower Normal Limit	Mean Change (SD) from Upper Normal Limit
Alanine aminotransferase (IU/L)	4 (4.0)	16	170.8 (50.92)		111.7 (48.15)
Aspartate aminotransferase (IU/L)	4 (4.0)	15	98.5 (40.51)		56.9 (38.57)
Bicarbonate (mmol/L)	3 (3.0)	3	12.7 (1.53)	-9.3 (1.53)	
Glucose (mmol/L)	2 (2.6)	5	8.1 (2.13)		2.6 (2.13)
Potassium (mmol/L)	2 (2.0)	4	4.3 (1.48)	-0.7 (0.21)	0.3 (0.00)
Albumin (g/L)	2 (2.0)	2	32.4 (8.98)	-8.0 (NA)	
Lymphocytes (10^9/L)	2 (2.0)	2	1.3 (0.21)	-0.3 (0.21)	

SD = standard deviation

8.5 Post-Market Adverse Reactions

The serious adverse reactions that have been reported include metabolic acidosis and pulmonary edema. Other adverse reactions that have been reported include abnormal body odor including from breath, skin, hair, and urine, retching and gagging, and dysgeusia or burning sensation in mouth.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

In vitro, PBA inhibited CYP2C9, CYP2D6, and CYP3A4/5. However, CYP3A4/5 showed differential inhibition by PBA, where metabolism of testosterone was inhibited, but metabolism of midazolam was not. PAA inhibited all of the tested CYPs, which included CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and both of CYP3A4/5 activities.

RAVICTI and/or its metabolites, PAA and PBA, have been shown to be weak inducers of CYP3A4 enzyme in vivo.

9.3 Drug-Behavioural Interactions

Interactions with behavioural risks have not been established.

9.4 Drug-Drug Interactions

Table 4: Established or Potential Drug-Drug Interactions

Proper name	Ref	Effect	Clinical comment
Midazolam	CT	Increased rate of metabolism, ~32% decrease in midazolam AUC	RAVICTI is a weak inducer of CYP3A4.
Probenecid	T	May increase plasma PAA and PAGN	May inhibit the renal excretion of metabolites of RAVICTI including PAGN.
Corticosteroids	T	Use of corticosteroids may cause the breakdown of body protein and increase plasma ammonia levels	Monitor ammonia levels closely when corticosteroids and RAVICTI are used concomitantly
Valproic acid	T	Hyperammonemia may be induced	Monitor ammonia levels closely when use of valproic acid is necessary in UCD patients.
Haloperidol	T	Hyperammonemia may be induced	Monitor ammonia levels closely when use of haloperidol is necessary in UCD patients.

Legend: AUC=area under the curve; CT=clinical trial; PAA=phenylacetate/phenylaceic acid; PAGN= phenylacetylglutamine; T=theoretical; UCD=urea cycle disorder

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

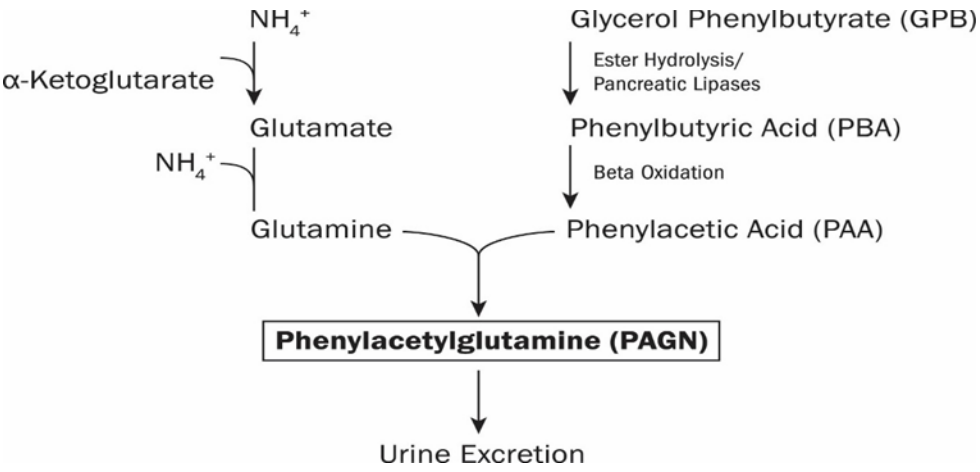
Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

UCDs are inherited deficiencies of enzymes or transporters necessary for the synthesis of urea from ammonia (NH_3, NH_4^+). Absence of these enzymes or transporters results in the accumulation of toxic levels of ammonia in the blood and brain of affected patients. RAVICTI is a triglyceride containing 3 molecules of PBA. PAA, the major metabolite of PBA, is the active moiety of RAVICTI. PAA conjugates with glutamine (which contains 2 molecules of nitrogen) via acetylation in the liver and kidneys to form PAGN, which is excreted by the kidneys (Figure 1). On a molar basis, PAGN, like urea, contains 2 moles of nitrogen and provides an alternate vehicle for waste nitrogen excretion.

Figure 1: RAVICTI Mechanism of Action



10.2 Pharmacodynamics

Pharmacological Effects: Blood ammonia was the pharmacodynamics efficacy surrogate in each of the short-term studies. In the combined pooled analysis of these short-term studies, daily average ammonia was 31 µmol/L in 80 adult and pediatric UCD patients during treatment with RAVICTI.

Cardiac Electrophysiology: A double-blind, randomized, placebo- and active-controlled, 4-arm crossover electrocardiogram (ECG) assessment study was performed in healthy subjects (N=57). Each subject received 4 treatments in a randomly assigned sequence: RAVICTI 4.4 g three times daily (TID), RAVICTI 6.6 g TID, placebo, and a positive control, each for 3 days. The 4.4 g TID and 6.6 g TID doses corresponded to average doses of 6.55 g/m^2/day and 9.62 g/m^2/day, respectively, which are within the therapeutic dose range. Serial ECG data were collected on day 3 of treatment between 0.5 and 23 hours after administration of the first of the TID doses.

RAVICTI resulted in a dose- and concentration-dependent increase in heart rate. At the 4.4 g TID dose, statistically significant ($p<0.05$) positive mean differences from placebo were observed at 4 of 12 time points on day 3, with a maximum mean difference from placebo of 4.6 bpm (90% confidence interval [CI] 3.0, 6.3) at the 12 h time point. At the 6.6 g TID dose, statistically significant positive mean differences from placebo were observed at 9 of 12 time points on day 3, with a maximum mean difference from placebo of 10.6 bpm (90% CI 8.3, 12.8) at the 16 h time point.

RAVICTI was also associated with QTcF (QTcF=QT/RR0.33) shortening. At the 4.4 g TID dose, statistically significant negative mean differences from placebo were observed at 9 of 12 time points on day 3, with a maximum mean difference from placebo of -7.2 ms (90% CI -10.1, -4.3) at the 16 h time point. At the 6.6 g TID dose, statistically significant negative mean differences from placebo were observed at 11 of 12 time points on day 3, with a maximum mean difference from placebo of -6.9 ms (90% CI -9.4, -4.4) at the 16 h time point.

10.3 Pharmacokinetics

Clinical Pharmacology:

In human studies, PBA, PAA, and PAGN were the major plasma metabolites and PAGN was the major urinary metabolite. An average of 60-70% of the PBA delivered as glycerol phenylbutyrate was excreted

in urine as PAGN, consistent with 60-70% bioavailability. Population pharmacokinetic modeling further indicated that PBA enters the circulation slowly when delivered orally as glycerol phenylbutyrate and that the rate of PAA to PAGN conversion varies directly with body surface area, resulting in a higher PAA exposure among young children as compared with adults for equivalent dosing.

Absorption

RAVICTI is a pro-drug of PBA. Upon oral ingestion, PBA is released from the glycerol backbone in the gastrointestinal tract by lipases. PBA derived from RAVICTI is further converted by β-oxidation to PAA.

In adult UCD patients receiving multiple doses of RAVICTI, the time to achieve the maximum plasma concentrations at steady state (T_{max-ss}) of PBA, PAA, and PAGN occurred at 8 h, 12 h, and 10 h, respectively, after the first dose in the day. In pediatric UCD patients receiving multiple doses of RAVICTI, the time to achieve the T_{max-ss} occurred at 8 h for all metabolites after the first dose in the day. The AUC_{0-24} for PBA in adult UCD patients was 433 µg·h/mL and for pediatric patients was 420 µg·h/mL. The AUC_{0-24} for PAA in adult UCD patients was 447 µg·h/mL and for pediatric patients was 1038 µg·h/mL. The AUC_{0-24} for PAGN in adult UCD patients was 1127 µg·h/mL and for pediatric patients was 1239 µg·h/mL. In adult UCD patients receiving multiple doses of RAVICTI mean maximum concentration (C_{max}) for PBA, PAA, and PAGN was 51.9 µg/mL, 38.5 µg/mL, and 78.6 µg/mL, respectively. In pediatric UCD patients receiving multiple doses of RAVICTI mean C_{max} for PBA, PAA, and PAGN was 62.7 µg/mL, 87.3 µg/mL, and 93.9 µg/mL, respectively. Total 24-hour urinary PAGN excretion in adult and pediatric UCD patients were 12.9 g and 12.5 g, respectively. The peak PAA concentrations in patients with UCDs in adults and in pediatric age groups (less than 2 months, 2 months to less than 2 years, 2 years to 17 years) are summarized in Table 5.

Table 5: Peak PAA Concentrations in Patients with UCDs Treated with RAVICTI in Clinical Trials

Age Range	RAVICTI Dose	Mean (SD) Peak PAA Concentration (µg/mL)	Median (Range) Peak PAA Concentration (µg/mL)
Less than 2 months (n=16)	3.1 to 12.7 mL/m^2/day (3.4 to 14 g/m^2/day)	257 (162)	205 (96 to 707)
2 months to less than 2 years (n=17)	3.3 to 12.3 mL/m^2/day (3.7 to 13.5 g/m^2/day)	142 (299)	35 (1 to 1215)
2 years to 17 years (n=53)	1.4 to 13.7 mL/m^2/day (1.5 to 15.1 g/m^2/day)	70 (79)	50 (1 to 410)
Adults (n=43)	0.6 to 14 mL/m^2/day (0.7 to 15.4 g/m^2/day)	39 (40)	25 (1.6 to 178)

PAA = phenylacetic acid; SD = standard deviation; UCD = urea cycle disorder

Distribution

In vitro, the extent of plasma protein binding for ^{14}C-labeled metabolites was 80.6% to 98.0% for PBA (over 1-250 µg/mL), and 37.1% to 65.6% for PAA (over 5-500 µg/mL). The protein binding for PAGN was 7% to 12% and no concentration effects were noted.

Metabolism

Upon oral administration, pancreatic lipases hydrolyze RAVICTI (i.e., glycerol phenylbutyrate), and release PBA. PBA undergoes β-oxidation to PAA, which is conjugated with glutamine in the liver and in the kidney through the enzyme phenylacetyl-CoA: L-glutamine-*N*-acetyltransferase to form PAGN. PAGN is subsequently eliminated in the urine.

Saturation of conjugation of PAA and glutamine to form PAGN was suggested by increases in the ratio of plasma PAA to PAGN with increasing dose and with increasing severity of hepatic impairment.

In in vitro studies, the specific activity of lipases for glycerol phenylbutyrate was in the following decreasing order: pancreatic triglyceride lipase, carboxyl ester lipase, and pancreatic lipase–related protein 2. Further, glycerol phenylbutyrate was hydrolyzed in vitro by esterases in human plasma. In these in vitro studies, a complete disappearance of glycerol phenylbutyrate did not produce molar equivalent PBA, suggesting the formation of mono- or bis-ester metabolites. However, the formation of mono- or bis-esters was not studied in humans.

Elimination

The mean (SD) percentage of administered PBA excreted as PAGN ranged from approximately 60-70% and averaged 68.9% (17.2) in adults and 66.4% (23.9) in pediatric UCD patients at steady state. PAA and PBA represented minor urinary metabolites, each accounting for <1% of the administered dose of PBA.

Special Populations and Conditions

- **Pediatrics:** Population pharmacokinetic modeling and dosing simulations suggest body surface area to be the most significant covariate explaining the variability of PAA clearance. PAA clearance was 10.9 L/h, 16.4 L/h, and 24.4 L/h, respectively, for UCD patients ages 3 to 5, 6 to 11, and 12 to 17 years.

  In pediatric patients with UCDs (n=14) ages 2 months to less than 2 years, PAA clearance was 6.8 L/h.

  In pediatric patients with UCDs (n=16) aged birth to less than 2 months, PAA clearance was 3.8 L/h. The mean peak ratio of PAA to PAGN in UCD patients aged birth to less than 2 months was higher (mean: 1.6; range 0.1 to 7.1) than that of UCD patients aged 2 months to less than 2 years (mean 0.5; range 0.1 to 1.2).

- **Sex:** In healthy adult volunteers, a gender effect was found for all metabolites, with women generally having higher plasma concentrations of all metabolites than men at any given dose level. In healthy female volunteers, mean C_{max} for PAA was 51% and 120% higher than in male volunteers after administration of 4 mL and 6 mL 3 times daily for 3 days, respectively. The dose normalized mean $AUC_{0\text{-}23h}$ for PAA was 108% higher in females than in males.

- **Hepatic Insufficiency:** No studies were conducted in UCD patients with hepatic impairment, although glycerol phenylbutyrate has been administered to over 100 patients with cirrhosis. Because conversion of PAA to PAGN occurs in the liver, patients with severe hepatic impairment may have reduced conversion capability and higher plasma PAA and plasma PAA to PAGN ratio. Therefore, dosage for patients with moderate to severe hepatic impairment should be started at the lower end of the recommended dosing range and should be kept on the lowest dose necessary to control their ammonia levels. A plasma PAA to PAGN ratio exceeding 2.5 may indicate saturation of PAA to PAGN conversion capacity and the need for reduced dosing.

- **Renal Insufficiency:** The pharmacokinetics of RAVICTI in patients with impaired renal function,

including those with end-stage renal disease (ESRD) or those on hemodialysis have not been studied.

11 STORAGE, STABILITY AND DISPOSAL

Store at 15-30°C.

Keep in original packaging to protect from light.

Use the contents of the bottle within 90 days after opening.

12 SPECIAL HANDLING INSTRUCTIONS

RAVICTI should be prescribed by a physician experienced in the management of urea cycle disorders.

Instruct patients to use the RAVICTI bottle and oral syringe as follows:

- Use a new reclosable bottle cap adapter with each new bottle that is opened.
- Open the RAVICTI bottle and twist on the new reclosable bottle cap adapter.
- Use a new and dry oral syringe to withdraw each prescribed dose of RAVICTI.
- Discard the oral syringe after each dose.
- Tightly close the tethered tab on the reclosable bottle cap adapter after each use.
- Do not rinse the reclosable bottle cap adapter.
- If water or moisture enters the RAVICTI bottle, the contents will become cloudy in appearance. If the contents of the bottle appear cloudy at any time, do not use the remaining RAVICTI in the bottle and return it to the pharmacy or patient program to be discarded.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

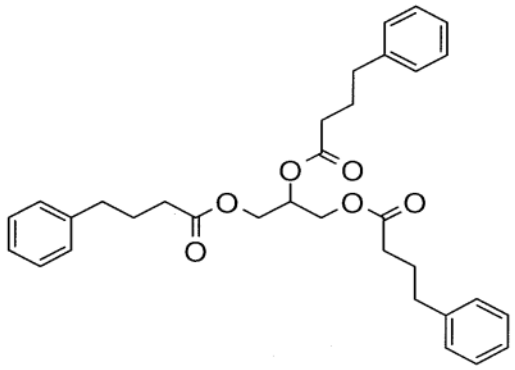
Drug Substance

Proper name: glycerol phenylbutyrate

Chemical name: benzenebutanoic acid, 1',1''–(1,2,3-propanetriyl) ester

Molecular formula and molecular mass: $C_{33}H_{38}O_6$, 530.67

Structural formula:



Physicochemical properties: RAVICTI (glycerol phenylbutyrate) is a clear, colorless to pale yellow oral liquid. It is insoluble in water and most organic solvents, and it is soluble in dimethylsulfoxide (DMSO) and >65% acetonitrile.

Glycerol phenylbutyrate is a nitrogen-binding agent. It is a triglyceride containing 3 molecules of PBA linked to a glycerol backbone. The pH cannot be accurately determined due to the absence of any ionizable functional groups in the molecular structure.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Table 6: Summary of Patient Demographics for Clinical Trials in Urea Cycle Disorders

Study #	Study design	Dosage (Range), route of administration and duration	Study subjects, UCD subtype (n = number	Mean age (Range) Years	Sex
N/A	Pooled long-term population	11 (1-34) g/day	n=100 ARG: 2 ASL: 13 ASS: 12 CPS: 1 HHH: 3 OTC: 69	29 (0.2-60)	67% F

Study #	Study design	Dosage (Range), route of administration and duration	Study subjects, UCD subtype (n = number	Mean age (Range) Years	Sex
003	Open label, fixed sequence, switch over	13 (7-19) g/day oral 1 week	n=14 ASS: 1 HHH: 1 OTC: 8	36 (21-73)	60% F
006	Randomized, double blind, crossover	13 (2-34) g/day oral 2 weeks	n=45 ASS: 3 CPS: 2 OTC: 40	33 (18-75)	69% F
005	Open label, fixed sequence, switch over with 12-month safety extension	SO: 12 (8-19) g/day oral 1 week SE: 11 (2-19) g/day oral 12 months	SO: n=11 ASL: 1 ASS: 1 OTC: 9 SE: n=17 ASL: 1 ASS: 2 OTC: 14	SO: 10 (6-11) SE: 10 (6-11)	SO: 91% F SE: 82% F
007	Open label	13 (2-34) g/day oral 12 months	N=60 ARG: 1 ASL: 2 ASS: 4 CPS: 1 HHH: 3 OTC: 49	29 (6-60)	68% F
012	Open label, fixed sequence, switch over with 12-month safety extension	SO: 5 (1-9) g/day oral, 1 week SE: 5 (1-9) g/day oral 12 months	SO: 15 ARG: 1 ASL: 8 ASS: 3 OTC: 3 SE: 23 ARG: 1 ASL: 10 ASS: 6 OTC: 6	SO: 3 (0.2-5) SE: 3 (0.2-5)	SO: 53% F SE: 52% F

Study #	Study design	Dosage (Range), route of administration and duration	Study subjects, UCD subtype (n = number	Mean age (Range) Years	Sex
011	Open label safety extension	Adult: 11 (2-23) g/day oral, 643 days Pediatric: 7 (2-18) g/day oral, 467 days	Adult: 43 ARG: 1 ASL: 2 ASS: 2 HHH: 3 OTC: 35 Pediatric: 45 ARG: 1 ASL: 11 ASS: 7 OTC: 26	Adult: 33 (19-61) Pediatric: 7 (1-17)	Adult: 61% F Pediatric: 71% F
009	Open label	Age 2 months to <2 years: 4 (2-6) g/day oral, 9 months Age birth to <2 months: 2 (1-4) g/day oral, 10 months	2 months to <2 years: 10 ARG: 1 ASL: 3 ASS: 2 CPS: 2 OTC: 2 Birth to <2 months: 16 ASL: 1 ASS: 7 OTC: 8	2 months to <2 years: 9.87 (4.3-20.8) months Birth to <2 months: 0.83 (0.1-2) months	2 months to <2 years: 50% F Birth to <2 months: 44% F

Legend: ARG=arginase; ASL=argininosuccinate lyase; ASS=argininosuccinate synthetase; CPS=carbamyl phosphate synthetase; f=female; HHH=ornithine translocase deficiency; N/A=not applicable; OTC=ornithine transcarbamylase; SO =switch over; SE=safety extension.

The effectiveness of RAVICTI in controlling ammonia in patients with UCDs was evaluated in 114 UCD patients across four short-term switch over (SO) controlled studies (1 to 2 week) and three long term studies (12 month). The short-term studies enrolled 85 UCD patients (59 adult and 26 pediatric) and the long-term studies enrolled 126 UCD patients (51 adults and 75 pediatric). Most patients in the short-term studies also participated in the long-term studies. Demographic characteristics of the patient population are shown in Table 6.

HPN-100-003 (Study 003) was an open label, fixed-sequence, switch over study to compare control of blood ammonia on RAVICTI to sodium phenylbutyrate in 10 adult UCD patients (see Table 6) who were being treated with sodium phenylbutyrate for control of their UCD. Patients were enrolled and received sodium phenylbutyrate for 1 week and then switched to RAVICTI for 1 week. Each patient received sodium phenylbutyrate or RAVICTI TID with meals. The dose of RAVICTI was calculated to deliver the same amount of PBA as the dose of sodium phenylbutyrate. After 1 week of dosing with each treatment, all patients underwent 24 hours of ammonia measurements as well as blood and urine pharmacokinetics. Dietary protein was controlled throughout the study.

HPN-100-006 (Study 006) was a randomized, double-blind, double dummy, active-controlled, cross-over study to assess the non-inferiority of RAVICTI to sodium phenylbutyrate by evaluating blood ammonia in 45 adult UCD patients (see Table 6) who were being treated with sodium phenylbutyrate for control of their UCD. Each patient was randomized 1:1 to one of two treatment arms to receive either sodium phenylbutyrate/RAVICTI placebo → sodium phenylbutyrate placebo/RAVICTI or RAVICTI/sodium phenylbutyrate placebo → RAVICTI placebo/sodium phenylbutyrate for 4 weeks (2 weeks each on active sodium phenylbutyrate or RAVICTI). Each patient received sodium phenylbutyrate or RAVICTI TID with meals. The dose of RAVICTI was calculated to deliver the same amount of PBA as the sodium phenylbutyrate dose. After 2 weeks of dosing, by which time patients had reached steady state on each treatment, all patients underwent 24 hours of ammonia measurements. Dietary protein was controlled throughout the study. Upon completion of Study 006, patients were allowed to enroll into a separate long-term (12-month) open label study HPN-100-007 (Study 007).

Studies HPN-100-005 (Study 005) and HPN-100-012 (Study 012) were open label, fixed-sequence, switch over studies to compare control of blood ammonia on RAVICTI to sodium phenylbutyrate in 11 and 15 pediatric UCD patients, respectively (see Table 6). In each study, patients who were being treated with sodium phenylbutyrate for control of their UCD were enrolled and received sodium phenylbutyrate for 1 week and then switched to RAVICTI for 1 week. Each patient received sodium phenylbutyrate or RAVICTI TID with meals. The dose of RAVICTI was calculated to deliver the same amount of PBA as the dose of sodium phenylbutyrate. Three times or four times daily feeding and administration of RAVICTI was recommended; however, flexibility was allowed based on the subject's prior sodium phenylbutyrate dosing regimen and/or feeding habits. After 1 week of dosing with each treatment, all patients underwent 24 hours of ammonia measurements as well as blood and urine pharmacokinetics. Dietary protein was controlled throughout the study. Upon completion of the switch over part of each study, patients were allowed to continue receiving RAVICTI and new additional patients were allowed to enrol to receive RAVICTI for 12 months in an open label safety extension.

Study HPN-100-011 (Study 011) was an open-label, long-term study conducted to assess ammonia control in adult and pediatric patients with UCDs. The study enrolled patients with UCDs who had completed Studies 007, 005, and 012. Venous ammonia levels were monitored at a minimum of every 6 months.

Study HPN-100-009 (Study 009) was an uncontrolled, open label study in pediatric patients less than 2 years of age. The primary efficacy endpoint was successful transition to RAVICTI within a period of 4 days followed by 3 days of observation for a total of 7 days, where successful transition was defined as no signs and symptoms of hyperammonemia and a venous ammonia level less than 100 micromol/L. Ammonia levels were monitored for up to 4 days during transition and on day 7.

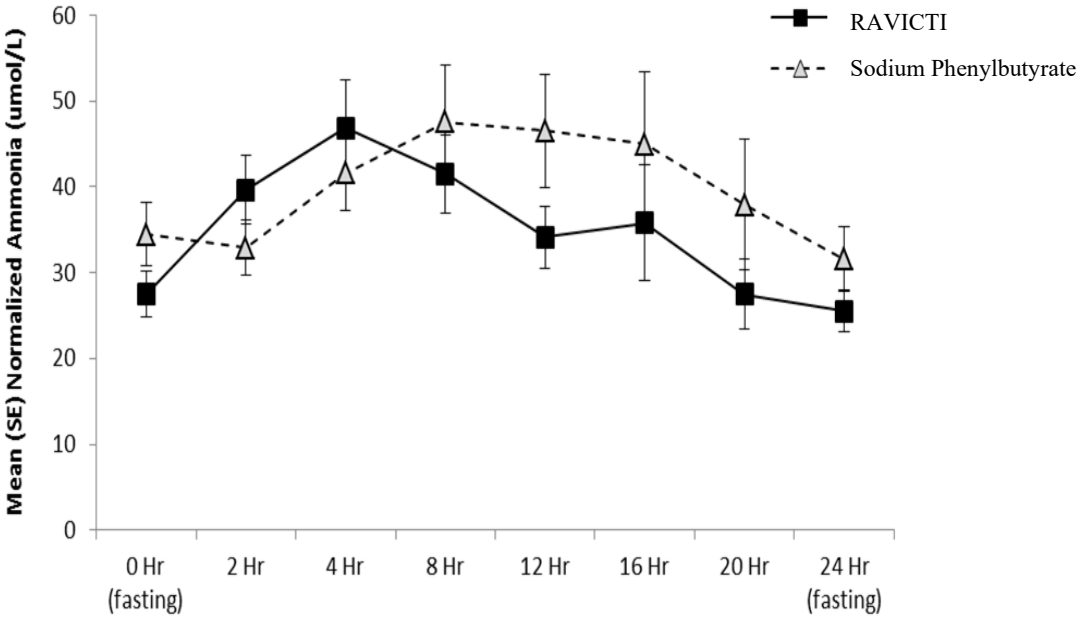
14.2 Study Results

14.2.1 Clinical Studies in Adult Patients with UCDs

Short Term Efficacy in Adult UCD Patients

In the pooled analysis of the short-term studies in adults (Figure 2), mean daily ammonia level was 34 µmol/L versus 40 µmol/L on sodium phenylbutyrate (p=0.136 paired t-test) and glutamine level was 760 µmol/L versus 807 µmol/L on sodium phenylbutyrate during treatment with RAVICTI (n=54). The maximum PAA and PAGN concentrations achieved during treatment with RAVICTI were 38.5 µg/mL and 78.6 µg/mL, respectively versus 91.5 µg/mL and 86.3 µg/mL on sodium phenylbutyrate, respectively.

Figure 2: Venous Ammonia Response in Adult UCD Patients in Short-Term Treatment

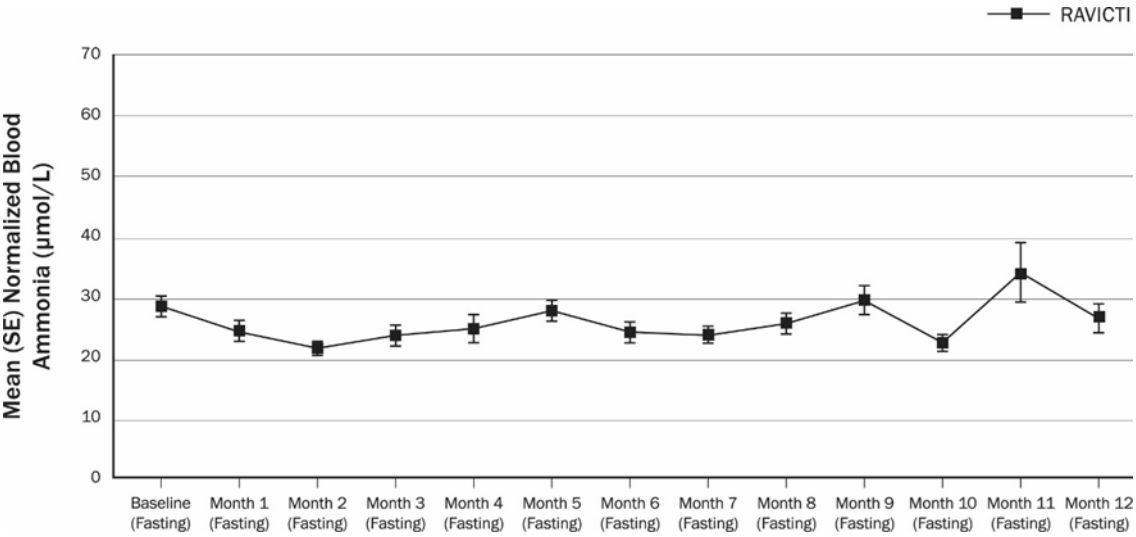


Long Term Efficacy in Adult UCD Patients

A long-term (12-month), uncontrolled, open-label study (Study 007) was conducted to assess monthly ammonia control and hyperammonemic crisis over a 12-month period. A total of 51 adults were in the study and all but 6 had been converted from sodium phenylbutyrate to RAVICTI. Venous ammonia levels were monitored monthly. Mean fasting venous ammonia values in adults were within normal limits during long-term treatment with RAVICTI (range: 6-30 µmol/L).

In long term studies, the median (25-75 percentiles) levels of PBA, PAA, and PAGN obtained from 195 samples in 51 adult patients were 0.5 (0.5-2.78) µg/mL, 1.12 (0.5-4.17) µg/mL, and 14.28 (4.64-28.15) µg/mL, respectively. Of 51 adult patients participating in the 12-month, open-label treatment with RAVICTI, 7 patients (14%) reported a total of 10 hyperammonemic crises versus 15 crises in 9 (18%) patients in the preceding 12 months prior to study entry, in patients receiving sodium phenylbutyrate. The fasting venous ammonia measured during Study 007 is displayed in Figure 3. Ammonia values across different laboratories were normalized to a common normal range of 9 to 35 µmol/L.

Figure 3: Venous Ammonia Response in Adult UCD Patients in Long-Term Treatment



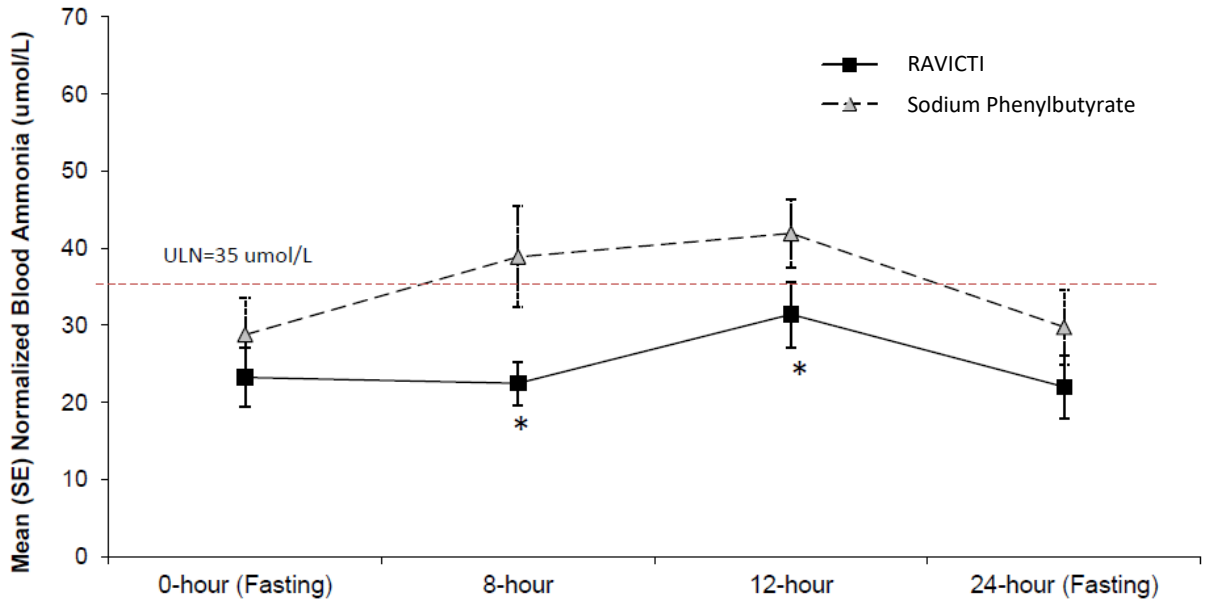
14.2.2 Clinical Studies in Pediatric Patients 2 Years to 17 Years of Age with UCDs

Short Term Efficacy in Pediatric Patients (2 years to 17 years of age) with UCDs

In the pooled analysis (Figure 4) of the short-term studies in children (005 and 012), mean daily ammonia level was 24 µmol/L versus 35 µmol/L on sodium phenylbutyrate (p=0.007; paired t-test) and glutamine level was 661 µmol/L versus 710 µmol/L on sodium phenylbutyrate during treatment with RAVICTI (N=26). Four patients <2 years of age are excluded for this analysis due to insufficient data. The maximum PAA and PAGN concentration achieved during treatment with RAVICTI were 87.3 µg/mL and 93.9 µg/mL, versus 50.2 µg/mL and 74.6 µg/mL on sodium phenylbutyrate, respectively.

Neuropsychological function was assessed as an exploratory endpoint at baseline and at the end of long-term treatment using BRIEF (Behavior Rating Inventory of Executive Function), CBCL (Child Behavior Checklist) and WASI (Wechsler Abbreviated Scale of Intelligence). CBCL and WASI scores remained stable while mean (SD) of T score in global executive composite of BRIEF improved significantly from 66.2 (14.02) at baseline to 56.5 (9.71) at the end of study.

Figure 4: Venous Ammonia Response in Pediatric Patients (2 years to 17 years of age) with UCDs in Short-Term Treatment

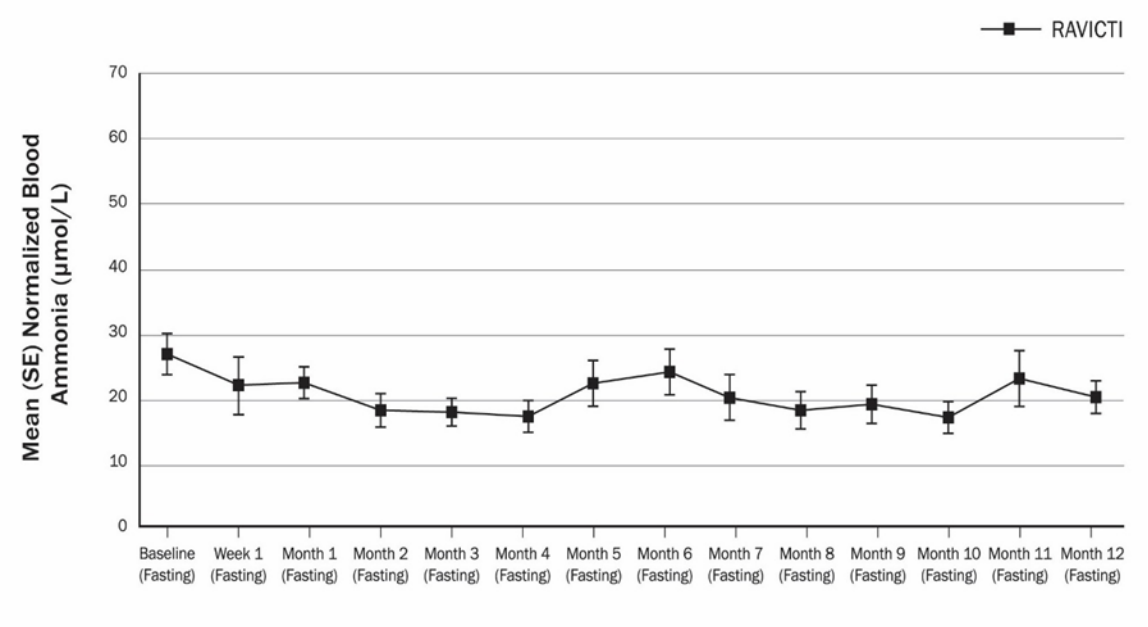


Long Term Efficacy in Pediatric Patients (2 years to 17 years of age) with UCDs

Long-term (12-month), uncontrolled, open-label studies were conducted to assess monthly ammonia control and hyperammonemic crisis over a 12-month period in three studies (Study 007, which also enrolled adults, extension of Study 005, and extension study 012). A total of 49 children ages 2 month to 17 years were enrolled, and all but 1 had been converted from sodium phenylbutyrate to RAVICTI. The fasting venous ammonia measured during these long-term studies in patients 2 years to 17 years is displayed in Figure 5 (range:17-25 µmol/L). Ammonia values across different laboratories were normalized to a common normal range of 9 to 35 µmol/L.

In long-term studies, the median (25-75 percentiles) levels of PBA, PAA, and PAGN obtained from 250 samples in 49 pediatric patients were 2.07 (0.5-8.7) µg/mL, 2.95 (0.5-31.19) µg/mL, and 21.18 (7.14-52.56) µg/mL, respectively. Of the 49 pediatric patients treated with RAVICTI for up to 12 months, 12 patients (24.5%) reported a total of 17 hyperammonemic crises versus 38 crises in 21 (42.9%) patients in the preceding 12 months prior to study entry, in patients receiving sodium phenylbutyrate.

Figure 5: Venous Ammonia Response in Pediatric Patients (2 years to 17 years of age) with UCDs in Long-Term Treatment



14.2.3 Clinical Studies in Pediatric Patients Less Than 2 Years of Age with UCDs

The efficacy of RAVICTI in pediatric patients less than 2 years of age with UCDs was evaluated in uncontrolled, open label studies (Studies 009, 011, and 012). A total of 17 pediatric patients with UCDs aged 2 months to less than 2 years participated in Studies 009, 011, and 012. Study 009 enrolled 16 pediatric patients less than 2 months of age.

Pediatric Patients Less than 2 Months of Age

A total of 16 pediatric patients less than 2 months of age participated in Study 009. Ten of the 16 patients transitioned from sodium phenylbutyrate to RAVICTI within 3 days of treatment and their initial dosage of RAVICTI was calculated to deliver the same amount of phenylbutyrate as the sodium phenylbutyrate dosage administered prior to RAVICTI dosing. Three of the 16 patients were treatment-naïve and started RAVICTI at dosages of 9.0, 9.4, and 9.6 mL/m^2/day. The remaining 3 of the 16 patients transitioned from intravenous sodium benzoate and sodium phenylacetate to RAVICTI within 3 days of treatment and their initial dosages of RAVICTI were 10.4, 10.9, and 10.9 mL/m^2/day.

Of the 16 patients, 16, 14, 12, 6, and 3 patients were treated for 1, 3, 6, 12, and 18 months, respectively.

After the initial 7-day transition period, patients received a mean RAVICTI dosage of 8 mL/m^2/day (8.8 g/m^2/day), with doses ranging from 3.1 to 12.7 mL/m^2/day (3.4 to 14 g/m^2/day). The frequency of dosing varied throughout the study. The majority of patients (n = 12) were dosed three times per day with feeding. No patients discontinued during the 7-day transition phase. Ammonia values across different laboratories were normalized (transformed) to a common normal pediatric range of 28 to 57 micromol/L for comparability.

During the safety extension phase (months 1-24), venous ammonia levels were monitored monthly for the first 6 months of treatment and every 3 months thereafter until the patients terminated or completed the study. During the safety extension phase, 1 patient discontinued from the study due to an adverse event (increased hepatic enzymes), 2 patients were withdrawn from the study by their parent/guardian, and 4 patients discontinued from the study early to undergo a liver transplant (protocol-defined discontinuation criterion). The normalized ammonia levels in pediatric patients less than 2 months of age, with available values (which varied by month of treatment) in Study 009 are shown in Table 7. Five patients (all less than 1 month of age) experienced a total of 7 hyperammonemic crises defined as in Studies 011 and 012. Hyperammonemic crises were precipitated by upper respiratory tract infection (2 events), change in diet (1 event), or had no identified precipitating event (4 events).

Table 7: Ammonia[a] Levels in Pediatric Patients Less than 2 Months of Age with Urea Cycle Disorders during the Safety Extension of in Study 009

Month	N (patients with available ammonia level)	Normalized Ammonia (micromol/L)[b]	
		Mean (SD)	Median (Min, Max)
1	15	71 (52)	60 (18, 227)
2	11	58 (40)	50 (16, 168)
3	14	53 (34)	46 (11, 122)
4	11	94 (106)	64 (35, 407)
5	10	52 (18)	57 (27, 86)
6	9	49 (24)	42 (22, 91)
9	8	56 (34)	45 (22, 122)
12	6	35 (17)	36 (11, 60)
15	4	52 (12)	52 (39, 67)
18	3	64 (14)	63 (50, 78)
24	9	63 (29)	72 (23, 106)

SD = standard deviation; ULN = upper limit of normal

[a] Normalized ammonia (micromol/L) = ammonia readout in micromol/L x (35/ULN of a laboratory reference range specified for each assay)

[b] Normal range: 28 to 57 micromol/L.

Pediatric Patients 2 months to Less than 2 Years of Age

The integrated analyses for patients with UCDs 2 months to < 2 years of age included 17 patients from Study 009, Study 011 and Study 012. 7 patients were enrolled in Study 012 [4 patients who continued from the switch-over (SO) phase into the safety extension phase (SE) of Study 012 and an additional 3 patients new enrolled in the safety extension phase]. A total of 6 patients completed this study (one subject discontinued due to a serious adverse reaction) and enrolled in Study 011. These patients were then integrated with a total of 10 patients enrolled in Study 009.

The primary efficacy endpoint for Study 009 was the successful transition to RAVICTI with controlled ammonia (no clinical symptoms and ammonia < 100 µmol/L). Eligible paediatric patients with UCDs

entered Study 009 either as a newly diagnosed patient presenting with or without hyperammonemic crisis (HAC) or as a previously diagnosed patient stabilized on sodium phenylbutyrate (NaPBA). One of 10 patients aged 2 months to < 2 years entered the study in HAC while the remaining 9 patients were previously stabilized on NaPBA and successfully transitioned to RAVICTI. Transition to RAVICTI was to be complete within 7 days of enrollment. Seven patients aged 2 months to < 2 years entered Study Study 012 (SO or SE) on a stable dose of NaPBA and were switched (transitioned) to an equivalent PBA dose of RAVICTI.

The median RAVICTI dose was 3.5 mL/day and ranged from 1.50 to 7.15 mL/day. The median RAVICTI dose corrected for body surface area (BSA) was 7.86 mL/m2/day (8.64 g/m2/day) and ranged from 3.34 to 12.30 mL/m2/day (3.68 to 13.53 g/m2/day). Dosages were similar in the long-term extension of the Study 009 (median RAVICTI dose was 3.95 mL and ranged from 2.7 to 5.7 mL; the median RAVICTI dose corrected for BSA was 9.57 mL/m2/day [10.53 g/m2/day] and ranged from 6.3 to 11.3 mL/m2/day [6.9 to 12.4 g/m2/day]). The duration of RAVICTI therapy in the integrated analysis of the 2 months to < 2 years age group averaged 8.85 months with a range of 6 days to 18.4 months. The median duration of treatment was 6 months. In the long-term extension of Study 009, the median duration on treatment for the 10 patients in this age cohort was 9.33 months.

All 17 patients (100.0%) achieved successful transition to study drug (RAVICTI) by the end of the transition period with controlled ammonia (i.e., no clinical symptoms and ammonia < 100 µmol/L). On Day 1, mean normalized plasma ammonia was 58.29 µmol/L, with a mean change from Baseline of -43.34 µmol/L. By the end of the transition period, normalized plasma ammonia was 60.80 µmol/L, with a mean change from Baseline of -28.36 µmol/L.

The normalized ammonia levels in pediatric patients 2 months to less than 2 years of age, with available values (which varied by month of treatment) in are shown in Table 8. The average maximum ammonia level excluding HAC among all patients 2 months to < 2 years of age receiving RAVICTI was 141.7 µmol/L (range of 46.7 to 513.0 µmol/L).

Table 8: Ammonia[a] Levels in Pediatric Patients 2 months to Less than 2 Years of Age with Urea Cycle Disorders (Study 009, Study 011 and Study 012)

Month	N (patients with available ammonia level)	Normalized Ammonia (micromol/L)[b]	
		Mean (SD)	Min, Max
Baseline[c]	17	89 (63)	26, 287
1	16	63 (49)	14, 208
2	11	44 (24)	15, 78
3	13	62 (70)	11, 259
4	6	99 (42)	59, 163
5	3	56 (36)	18,89
6	8	40 (23)	14, 80
9	6	65 (56)	19, 170

Month	N (patients with available ammonia level)	Normalized Ammonia (micromol/L)[b]	
		Mean (SD)	Min, Max
12	6	31 (24)	10, 66
End of Study	6	36 (16)	15, 61

SD = standard deviation; ULN = upper limit of normal
[a] Normalized ammonia (micromol/L) = ammonia readout in micromol/L x (35/ULN of a laboratory reference range specified for each assay)
[b] Normal range: 28 to 57 micromol/L.
[c] Baseline ammonia is defined as the mean of ammonia values within seven days prior to Day 1 dosing. If multiple ammonia values exist within a day, the mean ammonia value is used.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

***Acute toxicity*:** Following a single oral administration, the minimum lethal dose of glycerol phenylbutyrate was 1200 mg/kg in rats and greater than 6500 mg/kg in monkeys.

***Repeated dose toxicity*:** Repeat-dose oral toxicity studies were conducted in mice, rats, and monkeys for up to 13, 26, and 52 weeks, respectively. Clinical signs of central nervous system effects (e.g., hypoactivity, impaired equilibrium, or impaired muscle coordination) were observed in all species studied. In a 13-week repeat-dose study in juvenile monkeys, clinical observations of inappetence, tremors, hypoactivity, impaired equilibrium, twitching, body pallor, and labored respiration were observed at doses of ≥1250 mg/kg/day (≥2 times the clinical dose of 8.195 g/m^2/day in pediatric patients, based on combined AUCs for PBA and PAA). Histopathological changes in the liver (centrilobular hepatocellular hypertrophy) and spleen (hemosiderosis and lymphoid depletion) were observed in rats and monkeys following chronic dosing with glycerol phenylbutyrate. The no-observed-adverse-effect levels (NOAELs) in the 26-week rat and 52-week monkey studies were below 650 mg/kg/day and 750 mg/kg/day (<3.2 times and <2 times the dose of 7.557 g/m^2/day in adult patients, based on the combined AUCs for PBA and PAA), respectively. The NOAEL in the 13-week study in juvenile monkeys was below 750 mg/kg/day (<1.2 times the dose of 8.195 g/m^2/day in pediatric patients, based on combined AUCs for PBA and PAA, respectively).

Carcinogenicity

In a 2-year carcinogenicity study in rats, glycerol phenylbutyrate caused a statistically significant increase in the incidence of pancreatic acinar cell adenoma, carcinoma, and combined adenoma or carcinoma at a dose of 650 mg/kg/day in males (3.4 times the dose of 7.557 g/m^2/day in adult patients, based on combined AUCs for PBA and PAA) and 900 mg/kg/day in females (8.4 times the dose of 7.557 g/m^2/day in adult patients, based on combined AUCs for PBA and PAA). The incidence of the following tumors was also increased in female rats at a dose of 900 mg/kg/day: thyroid follicular cell adenoma, carcinoma and combined adenoma or carcinoma, adrenal cortical combined adenoma or

carcinoma, uterine endometrial stromal polyp, and combined polyp or sarcoma. The dose of 650 mg/kg/day in male rats is 2.1 times the dose of 8.195 g/m^2/day in pediatric patients, based on combined AUCs for PBA and PAA. The dose of 900 mg/kg/day in female rats is 5.1 times the dose of 8.195 g/m^2/day in pediatric patients, based on combined AUCs for PBA and PAA. In a 26-week study in transgenic (Tg.rasH2) mice, glycerol phenylbutyrate was not tumorigenic at doses up to 1000 mg/kg/day.

Genotoxicity

Glycerol phenylbutyrate was not genotoxic in the Ames test, the in vitro chromosomal aberration test in human peripheral blood lymphocytes, or the in vivo rat micronucleus test. The metabolites PBA, PAA, PAGN, and phenylacetylglycine were not genotoxic in the Ames test or in vitro chromosome aberration test.

Reproductive and Developmental Toxicology

Glycerol phenylbutyrate administered orally before cohabitation and through mating and implantation had no effect on fertility or reproductive function in male and female rats at oral doses up to 900 mg/kg/day (approximately 5.9 times the dose of 7.557 g/m^2/day in adult patients, based on combined AUCs for PBA and PAA). A higher dose of 1200 mg/kg/day to males was associated with lower fetal viability in both treated and untreated females. A significant reduction in sperm count in the caudal epididymis of male rats also occurred at 1200 mg/kg/day (approximately 6.4 times the dose of 7.557 g/m^2/day in adult patients, based on combined AUCs for PBA and PAA).

In embryo-fetal development studies, glycerol phenylbutyrate was administered orally to pregnant rats and rabbits during the period of organogenesis. In rats, decreased fetal body weight, increased incidence of malformations (absent, short, or thread-like tail) and skeletal variations (supernumerary ribs and thickened ribs), and ossification delay were observed at doses of ≥650 mg/kg/day (≥5.7 times the dose of 7.557 g/m^2/day in adult patients, based on combined AUCs for PBA and PAA) in the presence of maternal toxicity. Neither maternal nor developmental toxicities were observed in rabbits up to the highest dose of 350 mg/kg/day. The developmental NOAELs were 300 and 350 mg/kg/day for rats and rabbits, or approximately 1.9 and 2.7 times the dose of 7.557 g/m^2/day in adult patients (based on combined AUCs for PBA and PAA), respectively.

In a pre- and postnatal development study, pregnant rats received oral doses of 300, 600, and 900 mg/kg/day glycerol phenylbutyrate from gestation day 7 through lactation day 20 (weaning). Maternal toxicity (reduced body weights and food consumption) was evident at 600 and 900 mg/kg/day. A slight increase in the duration of gestation was noted in dams receiving 900 mg/kg/day (approximately 7.4 times the dose of 7.557 g/m^2/day in adult patients, based on combined AUCs for PBA and PAA). Other than reduced pup body weights throughout the preweaning period in the 900 mg/kg/day group, there were no adverse effects on sexual maturation, learning and memory, and reproductive capacity of the F1 generation. The NOAEL for reproduction in the dams and for growth of F1 pups was 600 mg/kg/day (approximately 5.7 times the dose of 8.195 g/m^2/day in adult patients, based on combined AUCs for PBA and PAA).

Juvenile Toxicity

In a juvenile toxicity study, glycerol phenylbutyrate was administered to male and female rats from postpartum day 2 through mating and gestation at oral doses of 650, 900, and 1200 mg/kg/day. Terminal body weights were significantly reduced by more than 10% in both males and females at 900 and 1200 mg/kg/day. Learning, memory, and motor activity endpoints were not affected.

However, fertility (number of pregnant rats) was decreased by up to 27% at ≥650 mg/kg/day. Embryo-fetal toxicity (increased post-implantation loss and decreased fetal body weight) occurred at doses of ≥650 mg/kg/day and teratogenicity (absent or thread-like tail and umbilical hernia) was observed at doses of ≥900 mg/day (≥3 times the dose of 7.557 g/m^2/day in adult patients, based on combined AUCs for PBA and PAA). The NOAEL for general toxicity in the neonatal/juvenile rats was 650 mg/kg/day (approximately 1.6 times the dose of 8.195 g/m^2/day in pediatric patients, based on combined AUCs for PBA and PAA). The NOAELs for fertility and embryo-fetal development were below 650 mg/kg/day (<2.6 times the dose of 7.557 g/m^2/day in adult patients, based on combined AUCs for PBA and PAA).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

RAVICTI®

Glycerol Phenylbutyrate Oral Liquid

Read this carefully before you start taking **RAVICTI** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **RAVICTI**.

What is RAVICTI used for?

- RAVICTI (rah-VIK-tee) is a prescription medicine used for long-term management of high blood levels of ammonia (hyperammonemia) caused by a condition called 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 should only be prescribed by a healthcare professional experienced in the treatment of UCDs.
- RAVICTI is not to be used to treat acute (severe) high blood levels of ammonia in patients with UCDs.
- It is not known if RAVICTI is safe and effective for the treatment of *N*-acetylglutamate synthase (NAGS) deficiency.

How does RAVICTI work?

Patients with UCD are unable to get rid of ammonia that is normally produced in the body. RAVICTI works by helping the body to remove excess ammonia.

What are the ingredients in RAVICTI?

Medicinal ingredients: glycerol phenylbutyrate

Non-medicinal ingredients: none

RAVICTI comes in the following dosage forms:

Oral liquid, 1.1 g/mL

Do not use RAVICTI if:

- You are experiencing acute hyperammonemia.
- You are allergic to glycerol phenylbutyrate, phenylbutyric acid (PBA), phenylacetic acid (PAA), and/or phenylacetylglutamine (PAGN), and/or any component of the container
- You are breastfeeding.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take RAVICTI. Talk about any health conditions or problems you may have, including if you:

- have liver or kidney problems
- have heart 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.

While taking RAVICTI it is still possible to develop an acute episode of excess ammonia in your blood. This is a medical emergency, and medical assistance should be sought immediately. Symptoms may include nausea, vomiting, confusion, combativeness, slurred speech, difficulty walking, and even loss of consciousness. An infection can cause an episode of excess ammonia; therefore, if you develop a fever you should seek prompt medical assistance.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following medicines may change the effect of RAVICTI and you may need more frequent blood tests:

- Midazolam, corticosteroids, barbiturates, topiramate, carbamazepine, and some immunosuppressive and anti-cancer drugs.
- Probenecid: May interfere with the removal of RAVICTI from the body.
- Corticosteroids: Use of corticosteroids may cause the breakdown of body protein and increase ammonia levels in your blood.
- Valproic Acid and Haloperidol: May cause high blood ammonia.

How to take RAVICTI:

- Take RAVICTI exactly as your healthcare professional tells you. Check with your healthcare professional if you are not sure.
- Your healthcare professional will tell you how much RAVICTI to take and when to take it.
- Your healthcare professional may change your dose if needed.
- RAVICTI is an oral liquid that is taken by mouth using an oral syringe. Ask your healthcare professional for an oral syringe if you do not have one.
- Take RAVICTI with food or formula.
- Stay on the diet that your healthcare professional gives you.
- For infants: In an infant who is breastfeeding, give RAVICTI just before breastfeeding.

Patients are to use the RAVICTI bottle and oral syringe as follows:

- Use a new reclosable bottle cap adapter with each new bottle that is opened.
- Open the RAVICTI bottle and twist on the new reclosable bottle cap adapter.
- Use a new and dry oral syringe to withdraw each dose of RAVICTI.
- Throw away the oral syringe after each dose.
- Tightly close the tethered tab on the reclosable bottle cap adapter after each use.
- Do not rinse the reclosable bottle cap adapter.

If water or moisture enters the RAVICTI bottle, the contents will become cloudy. If the contents of the bottle look cloudy at any time, do not use the remaining RAVICTI in the bottle. Return it to the pharmacy or patient program to be thrown away.

For people who have a nasogastric or gastrostomy tube in place, RAVICTI should be given as follows:

- It is recommended that all patients who can swallow take RAVICTI orally, even those with nasogastric and/or gastrostomy tubes.
- For patients who cannot swallow, a nasogastric or gastrostomy tube can be used to give RAVICTI as follows:

- Use a new dry oral syringe to withdraw each prescribed dose of RAVICTI from the bottle.
- Place the tip of the syringe into the tip of the nasogastric or gastrostomy tube. Push the plunger of the syringe to give RAVICTI into the tube.
- Use a separate syringe to flush 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 tube into the stomach.
- If needed, flush the tube again with 10 mL of water or formula to clear the tube.

Usual dose:

The daily dose of RAVICTI will be based on your body surface area. The dose should be adjusted based on your protein tolerance and diet.

- The daily dose range of RAVICTI is 4.5 – 11.2 mL/m^2/day.
- Patients 2 years of age and older: The total daily dose should be divided into 3 equal amounts and given with each meal or feeding. Each dose should be rounded up to the nearest 0.5 mL.
  Patients less than 2 years: The total daily dose should be divided into 3 or more equal amounts and given with each meal or feeding. Each dose should be rounded up to the nearest 0.1 mL.
- You will need regular blood tests to determine the correct daily dose.

Overdose:

If you think you, or a person you are caring for, have taken too much RAVICTI, contact your healthcare professional, hospital emergency department, or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you missed a dose of this medication, take it as soon as you remember. But if it is almost time for your next dose, skip the missed dose and continue with your next scheduled dose. Go back to the regular dosing schedule. Do not take two doses at the same time.

What are possible side effects from using RAVICTI?

These are not all the possible side effects you may feel when taking RAVICTI. If you experience any side effects not listed here, contact your healthcare professional.

- Diarrhea, gas, stomach pain and discomfort, constipation, indigestion, heart burn
- Decreased appetite
- Vomiting, nausea
- Fatigue
- Headache
- Fever
- Dizziness
- Muscle or body shaking
- Irregular menstrual bleeding
- Skin odor
- Acne
- Cough

- Dehydration
- Irritability, anxiety

RAVICTI can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
Acidosis (high level of acid in the blood): Weight loss, fatigue, malaise, abdominal pain, unusual muscle pain, feeling dizzy or lightheaded, fast or irregular heartbeat, shortness of breath, feeling unusually cold, especially in arms and legs,		√	
Blood disorders: bruising or bleeding for longer than usual if you hurt yourself, fatigue and weakness, low energy, infections, fever, aches, pains and flu-like symptoms, irregular heartbeats, pale complexion, shortness of breath		√	
Urinary tract infection (infection in urinary system including kidneys, ureters, bladder and urethra): Pain or burning sensation while urinating, frequent urination, blood in urine, pain in the pelvis, strong smelling urine, cloudy urine		√	
RARE			
Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			√
Neurotoxicity (nervous system side effects): Sleepiness, weakness, lightheadedness, change in taste, problems with hearing, confusion, problems with memory, worsening neuropathy (numbness, tingling, or burning in your hands or feet), headache			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store RAVICTI between 15-30°C.

Keep in original packaging to protect from light.

Use the contents of the bottle within 90 days after opening.

Keep out of reach and sight of children.

If you want more information about RAVICTI:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.horizontherapeutics.ca, or by calling 1-844-380-7850.

This leaflet was prepared by Horizon Therapeutics Ireland DAC

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RAV-CA-PM-003(E)

Market Status in United States

Drug Databases (https://www.fda.gov/Drugs/InformationOnDrugs/)

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Home (index.cfm?resetfields=1) | Back to Search Results

Product Details for NDA 203284

RAVICTI (GLYCEROL PHENYLBUTYRATE)
1.1GM/ML
Marketing Status: Prescription

Active Ingredient: GLYCEROL PHENYLBUTYRATE
Proprietary Name: RAVICTI
Dosage Form; Route of Administration: LIQUID; ORAL
Strength: 1.1GM/ML
Reference Listed Drug: Yes
Reference Standard: Yes
TE Code:
Application Number: N203284
Product Number: 001
Approval Date: Feb 1, 2013
Applicant Holder Full Name: HORIZON THERAPEUTICS US HOLDING LLC
Marketing Status: Prescription
Patent and Exclusivity Information (patent_info.cfm?Product_No=001&Appl_No=203284&Appl_type=N)