PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr RAVICTI™

(glycerol phenylbutyrate) Oral Liquid

1.1 g/mL

Alimentary Tract and Metabolism Product (ATC Code: A16A X09)

Horizon Pharma Ireland Ltd.
Connaught House, 1st Floor
1 Burlington Road
Dublin 4 Ireland

Date of Preparation:
March 16, 2016

Submission Control No: 174219

Table of Contents

[Pr] RAVICTI™

(glycerol phenylbutyrate) Oral Liquid

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Oral Liquid, 1.1 g/mL	There are no nonmedicinal ingredients *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

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

RAVICTI (glycerol phenylbutyrate) is indicated for:

Use as a nitrogen-binding agent for chronic management of adult and pediatric patients ≥2 years of age with 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.

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

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 WARNINGS AND PRECAUTIONS, *Special Populations*).

Pediatrics

Patients < 2 Months of Age

The use of RAVICTI in this age group is contraindicated (see WARNINGS AND PRECAUTIONS, *Special Populations*).

Patients > 2 months and < 2 years of Age

The safety and efficacy of RAVICTI in this age group have not been established.

CONTRAINDICATIONS

RAVICTI is contraindicated in patients who are:

- hypersensitive to RAVICTI or its metabolites (phenylbutyric acid [PBA], phenylacetic acid [PAA], and phenylacetylglutamine [PAGN])
- <2 months of age
- breastfeeding

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 ACTION AND CLINICAL PHARMACOLOGY, *Cardiac Electrophysiology*). 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

Since the metabolism and excretion of RAVICTI involves the liver, RAVICTI should be used with caution in patients with hepatic insufficiency *(*see ACTION AND CLINICAL PHARMACOLOGY, *Hepatic Insufficiency)*.

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.

Pancreatic Insufficiency

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.

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.

Special Populations

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

Nursing Women: 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 CONTRAINDICATIONS).

Pediatrics

Patients <2 Months of Age: The use of RAVICTI in this age group is contraindicated. Children under 2 months of age may have immature pancreatic exocrine function that could impair RAVICTI hydrolysis and release of PBA as well as subsequent formation of PAA, the active moiety. If pancreatic and extrapancreatic lipases are insufficient for hydrolysis of RAVICTI in this age group, impaired absorption of PBA and hyperammonemia could occur.

Patients <2 Years of Age: The safety and efficacy of RAVICTI in this age group have not been established.

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 or renal function, or concomitant drug therapy.

Monitoring and Laboratory Tests: Adjustment may be based on monitoring of plasma ammonia, glutamine, urinary phenylacetylglutamine (UPAGN) and/or plasma PAA and PAGN as well as the ratio of plasma PAA to PAGN (see Recommended Dose and Dosage Adjustment).

ADVERSE REACTIONS

Adverse Drug 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).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials 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 is useful for identifying drug-related adverse events and for approximating rates.

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 1 shows the adverse reactions reported in ≥2% of patients receiving RAVICTI.

Table 1: Adverse Reactions Reported in ≥2% of UCD Patients in Clinical Trials

System Organ Class Preferred Term	Number (%) of Patient 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)
Diarrhoea	7 (8.8)	4 (4.0)
Dyspepsia	2 (2.5)	3 (3.0)
Flatulence	7 (8.8)	3 (3.0)
Gastroesophageal reflux disease	0	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)

Table 1: Adverse Reactions Reported in ≥2% of UCD Patients in Clinical Trials (continued)

System Organ Class Preferred Term	Number (%) of Patient in Pooled Studies	
	Short-Term Controlled Studies (N=80)	Long-Term Open-Label Studies (N=100)
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)

Less Common Clinical Trial Adverse Drug Reactions (<2%)

Table 2: Less Common Clinical Trial Adverse Drug Reactions (<2%)

System Organ Class Preferred Term	Overall (N=114)
Gastrointestinal disorders	
Abdominal discomfort	1 (0.9%)
Abnormal faeces	1 (0.9%)
Defaecation urgency	1 (0.9%)
Dry mouth	1 (0.9%)
Eructation	1 (0.9%)
Gastrointestinal pain	1 (0.9%)
Painful defaecation	1 (0.9%)
Steatorrhoea	1 (0.9%)
Stomatitis	1 (0.9%)
Musculoskeletal and connective tissue disorders	
Muscle spasms	1 (0.9%)
Nervous system disorders	
Dysgeusia	1 (0.9%)
Lethargy	1 (0.9%)
Paraesthesia	1 (0.9%)
Somnolence	1 (0.9%)

Table 2: Less Common Clinical Trial Adverse Drug Reactions (<2%) (continued)

System Organ Class Preferred Term	Overall (N=114)
Psychiatric disorders	
Confusional state	1 (0.9%)
Reproductive system and breast disorders	
Amenorrhoea	1 (0.9%)
Menstruation irregular	1 (0.9%)
Respiratory, thoracic and mediastinal disorders	
Dysphonia	1 (0.9%)
Oropharyngeal pain	1 (0.9%)
Throat irritation	1 (0.9%)
Vascular disorders	
Hot flush	1 (0.9%)

Abnormal Hematologic and Clinical Chemistry 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)	

Post-Market Adverse Drug Reactions

The serious adverse reactions are metabolic acidosis and pulmonary edema.

The non-serious adverse drug reactions are breath odor and urine odor abnormal.

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*.

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

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

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.

Recommended Dose and Dosage Adjustment

The recommended total daily dose range of RAVICTI 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:

- The total daily dose should be divided into equal amounts and given with each meal or feeding (e.g. three times to six times per day).
- Each rounded up to the nearest 0.5 mL.

The recommended starting dosages for patients switching from sodium phenylbutyrate to RAVICTI and patients naïve to PBA may be different.

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

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.

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

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 WARNINGS AND PRECAUTIONS, *Neurologic*). 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.

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 range.

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.

Administration

For oral administration.

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

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 an oral syringe to withdraw the prescribed dosage of RAVICTI from the bottle.
- Place the tip of the syringe into the tip of the gastrostomy/nasogastric tube.
- Administer RAVICTI into the tube.
- Flush with at least 10 mL of water or formula.

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.

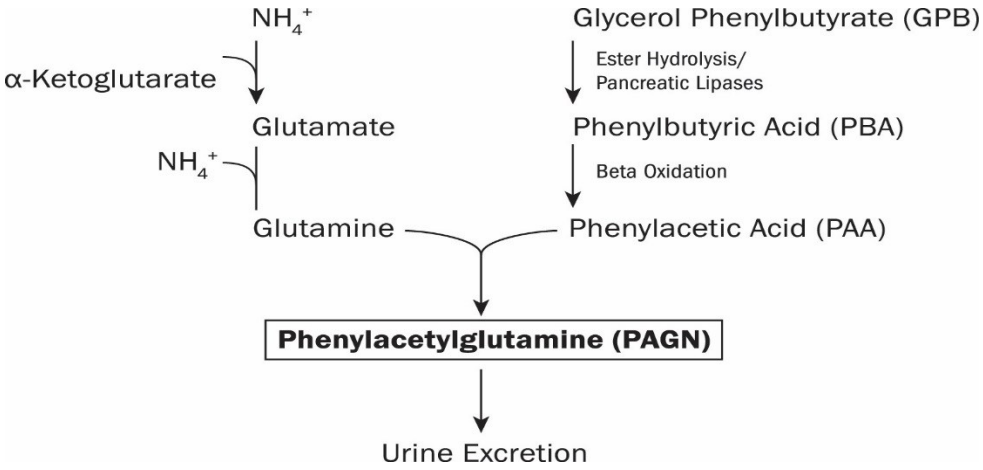
For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

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



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 ECG assessment study was performed in healthy subjects (N=57). Each subject received 4 treatments in a randomly assigned sequence: RAVICTI 4.4 g 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% 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..

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 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 8h, for all metabolites, after the first dose in the day. The AUC_{0-24} (µg·h/mL) for PBA in adult UCD patients was 433 and for pediatric patients was 420 respectively. The AUC_{0-24} (µg·h/mL) for PAA in adult UCD patients was 447 and for pediatric patients was 1038 respectively. The AUC_{0-24} (µg·h/mL) for PAGN in adult UCD patients was 1127 and for pediatric patients was 1239, respectively. 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-hr urinary PAGN excretion in adult and pediatric UCD patients were 12.9 and 12.5 g, respectively.

Distribution: *In vitro*, the extent of plasma protein binding for 14C-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.

Excretion: 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.

Gender: 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.

STORAGE AND STABILITY

Store at 15-30°C.

Keep in original packaging to protect from light.

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

RAVICTI is a colourless to pale yellow oral liquid. The dosage strength is 1.1 g/mL glycerol phenylbutyrate (delivers 1.02 g/mL of PBA). There are no excipients.

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

- Single 25-mL bottle per carton
- Four 25-mL bottles per carton

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

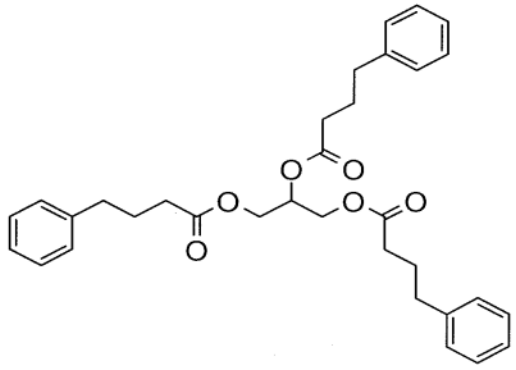
Proper name: RAVICTI

Common 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.

CLINICAL TRIALS

Study demographics and trial design

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 in 85 UCD patients (59 adult and 26 pediatric) and the long-term studies enrolled 100 UCD patients (51 adults and 49 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 5.

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 5) 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 pharmacokinetic (PK). 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 5) 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 three times a day (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 5). 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 PK. Dietary protein was controlled throughout the study. Upon completion of switch-over part of each study, patients were allowed to continue receiving and new additional patients were allowed to enrol to receive RAVICTI for 12 months in an open label safety extension.

Table 5: Summary of Patient Demographics for Clinical Trials in Urea Cycle Disorders

Study #	Trial design	Dosage (Range), route of administration and duration	Study subjects, UCD subtype (n = number)	Mean age (Range) Years	Gender
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
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

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

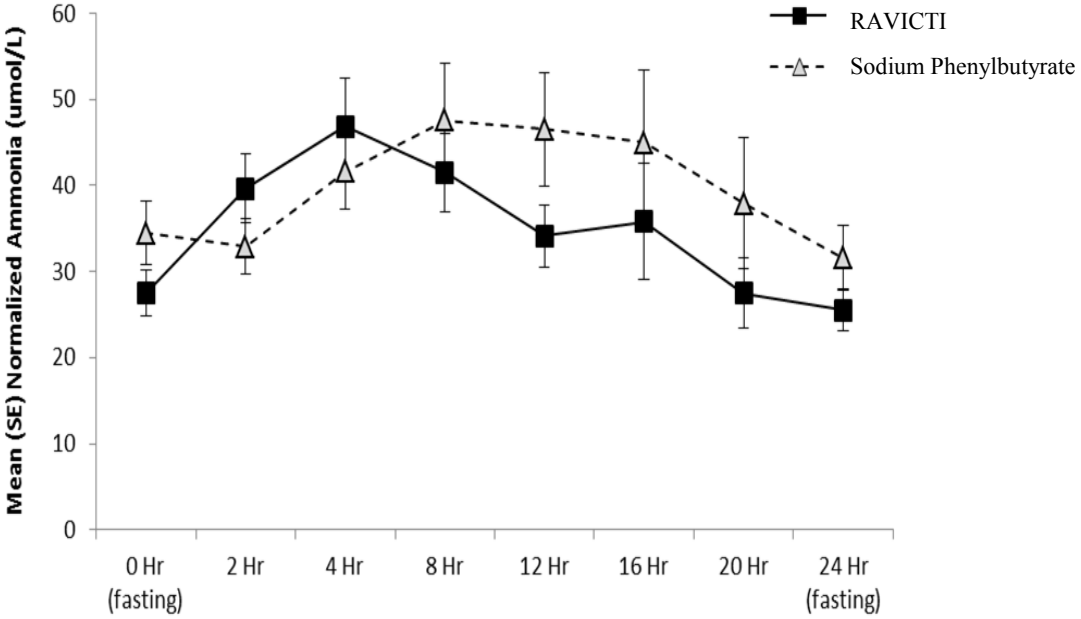
Study results

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



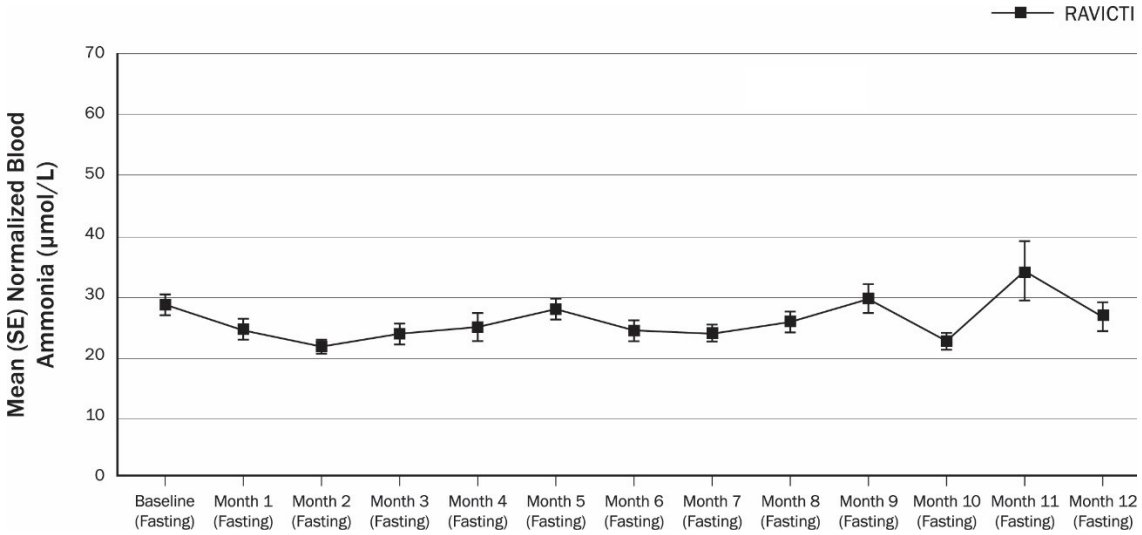
Long Term Efficacy in Adult UCD Patients

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



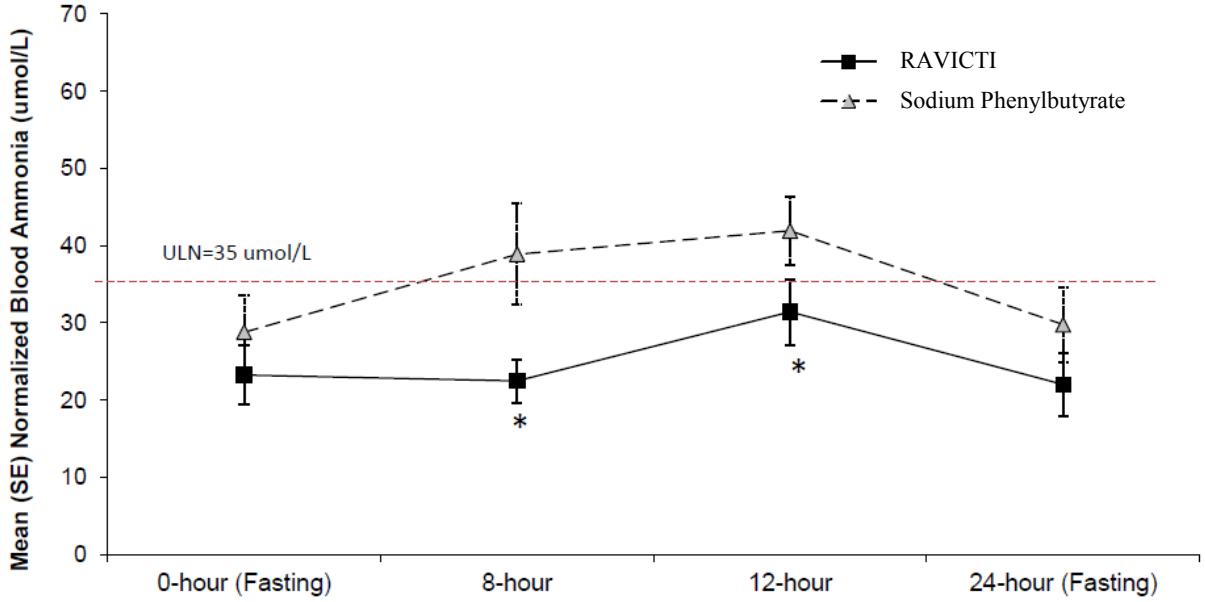
Clinical Studies in Pediatric Patients with UCDs

Short Term Efficacy in Pediatric UCD Patients

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 UCD Patients in Short-Term Treatment

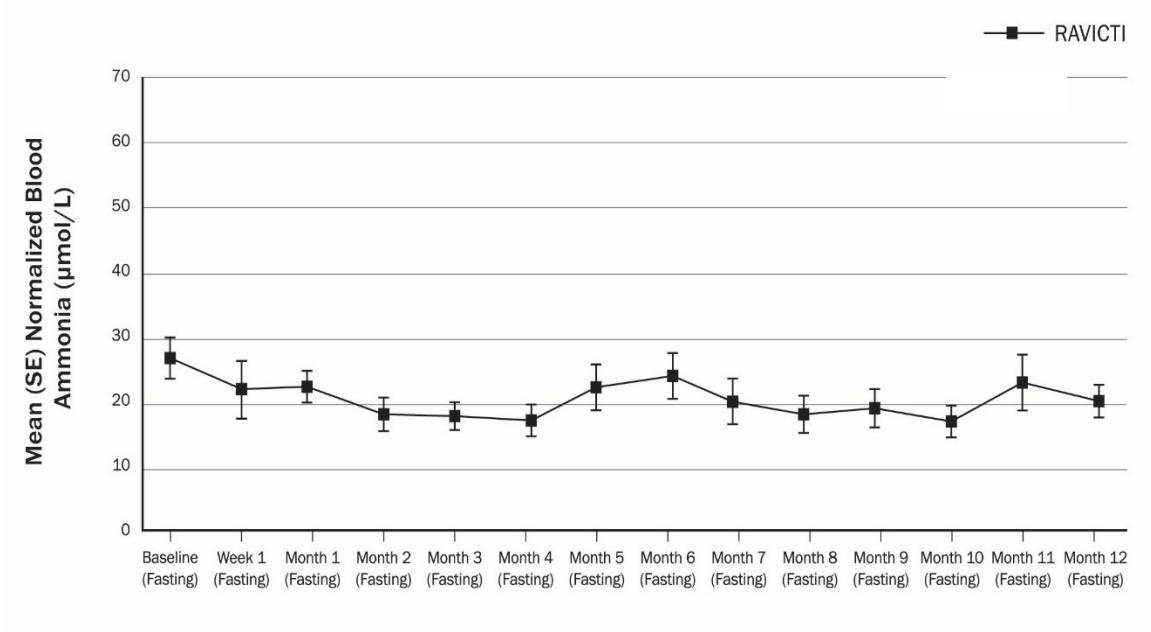


Long Term Efficacy in Pediatric UCD Patients

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 UCD Patients in Long-Term Treatment



DETAILED PHARMACOLOGY

Nonclinical Pharmacology

The nonclinical pharmacokinetics and toxicology studies established that glycerol phenylbutyrate was not detected in plasma, indicating that PBA is released from glycerol phenylbutyrate in the gastrointestinal tract and is subsequently converted systemically to PAA, the active molecule. Results of *in vitro* studies have shown that digestive lipases are the main enzymes responsible for hydrolysis of glycerol phenylbutyrate.

In a study in male monkeys, the average bioavailability of PBA following oral administration of glycerol phenylbutyrate was 67% (51-80%) with a mean T_{max} of 8 h, which may reflect the need to hydrolyze the ester functionality within the molecule prior to absorption. Concentrations of known metabolites PBA, PAA, and PAGN (representing about 30% of the administered dose) were quantifiable in the plasma of all three monkeys at 1.5 h postdose. Following a single oral dose of radiolabeled glycerol phenylbutyrate to male monkeys, radioactivity was widely distributed throughout the body. Tissue concentrations were highest in the large intestine wall, bile, plasma, kidney, liver, urinary bladder, and whole blood.

Systemic metabolites of glycerol phenylbutyrate are excreted primarily via the urine following oral administration to rats and primates. In primates and humans, the major pathway for excretion in urine is in the form of phenylactetyl glutamine which results from conjugation of PAA with glutamine, while in other animals, including rat, rabbit, and mouse, PAA is excreted in the urine conjugated with glycine.

Clinical Pharmacology

In human studies, PBA, PAA and PAGN were the major plasma metabolites and PAGN 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. PopPK

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.

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 (CNS) 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).

Carcinogenesis

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 7.557g/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 7.557g/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.

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.

Reproductive toxicity

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 7.557g/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 7.557g/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 7.557g/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 7.557g/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 F_1 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).

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 7.557g/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 7.557g/m^2/day in adult patients, based on combined AUCs for PBA and PAA).

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

Pr 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 in adults and children 2 years of age and older 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.

RAVICTI is not to be used in children less than 2 months of age. It is not known if RAVICTI is safe and effective in children between the ages of 2 months and 2 years.

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:

- Children are less than 2 months of age.
- You are experiencing acute hyperammonemia.

- You are allergic to glycerol phenylbutyrate, phenylbutyric acid (PBA), phenylacetic acid (PAA), and/or phenylacetylglutamine (PAGN).
- 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 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:

Usual dose:

The daily dose of RAVICTI will be based on your body surface area and 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.
- The total daily dose should be divided into equal amounts and given with each meal or feeding.
- Each dose should be rounded up to the nearest 0.5 mL.
- RAVICTI should be taken by mouth using an oral syringe that is provided to you by your pharmacist.

- You will need regular blood tests to determine the correct daily dose.
- Take RAVICTI exactly as your doctor tells you.
- Stay on the diet that your doctor gives you.

For people who have a nasogastric or gastric 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 gastric tubes.
- For patients who cannot swallow, a nasogastric or gastric tube can be used to administer RAVICTI as follows:
  - Use an oral syringe to take the prescribed dose of RAVICTI from the bottle.
  - Place the tip of the syringe into the tip of the nasogastric or gastric tube and administer RAVICTI into the tube.
  - Flush the nasogastric or gastric tube with at least 10 mL of water or formula.

Overdose:

If you think you 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.

The most common side effects include diarrhea, gas, headache, decreased appetite, vomiting, nausea, fatigue and skin odor.

Other side effects that may occur include:

- Stomach pain and discomfort, constipation, indigestion
- Dizziness
- Tremor
- Irregular menstrual bleeding
- Acne

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		Get immediate medical help
	Only if severe	In all cases	
RARE **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			√
Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			√

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 help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:
- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

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 (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website http://www.RAVICTI.CA, or by calling 1-855-823-7878.

Talk to your doctor about participating in a UCD registry. The purpose of this registry is to collect information about people with UCD to improve care.

This leaflet was prepared by Horizon Pharma Ireland Ltd.

Last Revised: MARCH-16-2016