

## Drug Class Review: Urea Cycle Disorders

**Date of Review: December 2024**

**Literature Search: 1/1/1990-10/8/24**

### **Purpose for Class Review:**

To review evidence related to agents treating urea cycle disorders (UCDs) to create a drug class and identify appropriate utilization management strategies.

### **Plain Language Summary:**

- This review looks at evidence for certain medicines that treat urea cycle disorders.
- When protein from food or muscle is used in the body, it creates a waste product of nitrogen.
- Urea cycle disorders are conditions that are caused when a person cannot remove waste nitrogen from the body. People with urea cycle disorders get sick when there is too much ammonia in the blood. Ammonia contains nitrogen. Too much ammonia can lead to confusion, permanent brain damage, and death. Many people with urea cycle disorders become sick as newborns or very young babies.
- People with urea cycle disorders are treated by monitoring food (protein) intake, taking certain amino acid (protein is made of amino acids) supplements, and sometimes taking drugs called nitrogen-scavengers. Nitrogen-scavengers help the body get rid of nitrogen so that the ammonia in the blood stays low. The only cure for a urea cycle disorder is a liver transplant.
- Sodium phenylbutyrate and glycerol phenylbutyrate are both nitrogen-scavengers that are taken by mouth. Sodium phenylbutyrate comes in several different forms (powder, granules, tablets).
- Evidence does not show one nitrogen-scavenger medicine to be better than another at keeping ammonia low or is safer. Some forms taste and smell better than others and can be easier to swallow.
- The Drug Use Research and Management group recommends placing the different nitrogen-scavengers in a class and assessing cost differences to determine if one drug should be preferred over another.

### **Research Questions:**

1. What is the comparative efficacy and effectiveness of nitrogen scavengers for the management of urea cycle disorders?
2. What are the comparative harms of nitrogen scavengers for the management of urea cycle disorders?
3. Are there subgroups of patients based on demographics (e.g., age, racial or ethnic groups, gender), other medications, or co-morbidities for which one nitrogen-scavenger is more effective or associated with fewer adverse events?

## Conclusions:

- There were no high-quality guidelines or systematic reviews identified.
- There is moderate quality evidence that glycerol phenylbutyrate is non-inferior to sodium phenylbutyrate for maintaining the ammonia level under 100 µmol/L.<sup>1-4</sup> Populations studied in the evidence base includes newborns to adults.
- There is insufficient evidence to support one product over another based on efficacy or safety.<sup>1-4</sup>
- There is insufficient evidence of different efficacy or harms for patient subgroups (e.g., age, racial or ethnic groups, gender).
- The Nutritional Supplements PA requires edits to align with recently updated Oregon Administrative Rule ([OAR 410-148-0260](#)).<sup>5</sup>

## Recommendations:

- Create preferred drug list class. Include autoPA to allow continuation of therapy for non-preferred agents after initial approval.
- After evaluation of costs in executive session, Pheburane<sup>®</sup> (sodium phenylbutyrate granules) and Buphenyl<sup>®</sup> and generics (sodium phenylbutyrate tablets and powder) were made preferred. Ravicti<sup>®</sup> (glycerol phenylbutyrate liquid) and Olpruva<sup>®</sup> (sodium phenylbutyrate pellet pack) were made nonpreferred on the PMPDP.
- The Nutritional Supplements PA will be updated to align with [OAR 410-148-0260](#).

## Background:

Urea cycle disorders are the result of a deficiency of an enzyme or cotransporter in the urea cycle pathway (**Table 1**), which is responsible for clearance of nitrogen from the body.<sup>6</sup> The inability to convert nitrogen to urea results in hyperammonemia in patients with UCD.<sup>6</sup> Complications of UCD are hyperammonemia, intellectual disability, or death.<sup>7</sup> Early symptoms in neonates are often poor feeding and vomiting, loss of thermoregulation, lethargy, and irritability which can worsen to more severe symptoms such as respiratory distress or life threatening manifestations including acute encephalopathy, cerebral edema, seizures, multiorgan failure, coma, and death.<sup>8</sup>

**Table 1.** Types of Urea Cycle Disorders<sup>9,10</sup>

Name	Alternate names	Urea Cycle Component
Arginase (ARG) deficiency	Hyperargininemia	Catalytic enzyme
Argininosuccinate Lyase (ASL) deficiency	Argininosuccinic Aciduria (ASA)	Catalytic enzyme
Argininosuccinate Synthase (ASS or ASS1) deficiency	Citrullinemia type I	Catalytic enzyme
Carbamoyl-phosphate Synthase (CPS1) deficiency		Catalytic enzyme
Citrin deficiency	Citrullinemia type II	Amino acid transporter
N-acetyl glutamate synthetase (NAGS) deficiency		Cofactor-producing enzyme
Ornithine Transcarbamylase (OTC) deficiency		Catalytic enzyme
Ornithine Translocase (ORNT1) deficiency	Hyperornithinemia-Hyperammonemia-Homocitrullinuria or HHH Syndrome	Amino acid transporter

Urea cycle disorders occur at an incidence of 1:35,000, though this can vary by specific type of enzyme disorder.<sup>6,7,11</sup> For example, ornithine transcarbamylase (OTC) deficiency has an estimated incidence of 1:56,500 compared to N-acetylglutamate synthase (NAGS) deficiency which occurs in < 1:2,000,000.<sup>6</sup> These disorders can present as neonatal or late onset UCD. Late onset forms can present at any time in life, usually in response to a significant metabolic stressor.<sup>10</sup>

People with complete defects usually present in the neonatal period.<sup>10</sup> Approximately 50% of cases present as neonatal hyperammonemia with a mortality rate of 25-50%.<sup>7,11</sup> The Oregon Newborn Screening is able to detect arginase deficiency (ARG), argininosuccinic aciduria (ASA), and citrullinemia, type I and II. The validity is greater than 99% for citrullinemia and ASA on the initial test.<sup>12</sup> A second test was needed to detect ARG deficiency in the only infant diagnosed in Oregon.<sup>12</sup>

Primary urea cycle disorders are caused by congenital deficiency urea cycle enzymes. The six urea cycle enzymes are: N- acetylglutamate synthase (NAGS), carbamoyl phosphate synthase I (CPS1), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS1), argininosuccinate lyase (ASL), and arginase (ARG).<sup>8</sup> Absence of activity or severe deficiency in CPS1, OTC, ASS1, or ASL (all catalytic enzymes) or NAGS (a cofactor producing enzyme) result in symptoms within days of birth.<sup>10</sup> Risk factors for UCD include consanguineous parents, males (OTC deficiency), and Asian race (citrin deficiency).<sup>6</sup>

Hyperammonemic crises can be triggered by many stressful conditions including birth, infections, fever, surgery, unusual protein load, and certain medications. Valproate and L-asparaginase/pegaspargase are the medications most associated with hyperammonemic crisis, but others, including topiramate, carbamazepine, phenobarbitone, phenytoin, primidone, furosemide, hydrochlorothiazide, and salicylates are also associated with this condition. Chemotherapy and high-dose glucocorticoids can also trigger crises.<sup>7,11</sup>

Ammonia levels are used as a surrogate for morbidity and mortality patients with UCDs.<sup>13</sup> There is an association between high ammonia levels and adverse neurological outcomes, coma, and death.<sup>13</sup> The Food and Drug Administration (FDA) has accepted ammonia levels as the primary endpoint for the approvals of both RAVICTI and CARBAGLU.<sup>13</sup> Additional outcomes of interest include hyperammonemic crises, quality of life, medication adherence, adverse events, and mortality. Given rarity of UCDs, large studies with clinical outcomes are difficult to perform.

Patients who survive initial neonatal hyperammonemic crises and those who present later in life must receive long-term management of the condition. This includes careful overall protein/calorie intake, amino acid supplementation, monitoring of appropriate intake of vitamin and minerals, and avoidance of catabolic triggers.<sup>7,11</sup> Liver transplantation can be a curative option for UCDs except NAGS deficiency.<sup>7</sup> Most UCDs require supplementation of various amino acids, including L-arginine and/or L-citrulline.<sup>7</sup> Supplements are approved differently than regular drugs which have gone through specific testing and FDA approval, and may not be federally rebatable. The policy for nutritional supplements is determined by Home Enteral/Parenteral Nutrition and IV Services (EPIV) and detailed in OAR 410-148-0260.<sup>5</sup> This OAR was updated in August 2024. Criteria differ for adults and for individuals who fall under the early and periodic screening, diagnostic, and treatment (EPSDT) benefit, but generally both populations must be assessed by a registered dietician or treating provider annually for ability to meet their recommended caloric/protein or micronutrient needs through regular, liquified, blenderized, or pureed foods in any modified texture or form with documentation that oral nutritional formula and/or supplement are integral for the treatment of nutritional deficiencies associated with certain specified conditions (**Table 2**). The Nutritional Supplements prior authorization for the Oregon Health Plan (OHP) Fee-for-service (FFS) population will be edited to align with current rules.<sup>5</sup>

**Table 2. Approved conditions for nutritional deficiencies (OAR 410-148-0260)<sup>5</sup>**

Diagnosed acute or chronic malnutrition
Documentation of weight, either currently or historically, supported by oral nutritional supplements
Increased metabolic need resulting from severe trauma
Malabsorption difficulties (e.g., short-gut syndrome, fistula, cystic fibrosis, renal dialysis)

Inborn errors of metabolism (e.g., fructose intolerance, galactosemia, maple syrup urine disease [MSUD], or phenylketonuria [PKU])
Ongoing cancer treatment, advanced Acquired Immune Deficiency Syndrome (AIDS) or pulmonary insufficiency
Oral aversion or other psychological condition making it difficult for a client to consume their recommended caloric/protein or micronutrient needs through regular, liquified, blenderized, or pureed foods in any modified texture or form

Pharmacologic outpatient treatment of UCDs is primarily limited to ammonia scavenging drugs. These medications provide an alternate pathway for excretion of nitrogen waste from the body. The inability to excrete nitrogen results in accumulation of ammonia (NH<sub>3</sub>). Combination sodium benzoate/sodium phenylacetate became available in the 1980's and is only available as an injectable formulation in the United States. Phenylacetate conjugates with glutamine (which contains 2 molecules of nitrogen) via acetylation in the liver and kidneys to form phenylacetylglutamine, which is excreted by the kidneys.<sup>14</sup> The phenylacetate was edited to its precursor phenylbutyrate which has a less noxious odor.<sup>15</sup> Phenylbutyrate is oxidized to phenylacetate.<sup>14</sup> Sodium phenylbutyrate (NaPBA) became available as a single product in 1983,<sup>15</sup> however it is generally considered unpalatable, particularly to young children. Several different formulations, with the intent to improve taste and smell have been introduced in recent years. Other adverse qualities of NaPBA are high pill burden and sodium content.<sup>15</sup> The maximum daily dosage of NaPBA (20g; 40 tablets) contains ~ 2400 mg sodium.<sup>15</sup> To circumvent issues related to palatability, sodium content and pill burden, glycerol phenylbutyrate (GPB) was developed, containing 3 molecules of phenylbutyrate on a glycerol backbone.<sup>15</sup> It requires pancreatic lipase hydrolysis to release the phenylbutyrate molecules.<sup>15</sup> Pancreatic insufficiency or intestinal malabsorption limit effectiveness of GPB. Neither NaPBA or GPB are approved to treat NAGS deficiency.<sup>14,16</sup> Carglumic acid (CARBAGLU) is approved for treatment of NAGS deficiency and not included in this evidence review. Four patients in Oregon Medicaid have received a nitrogen-scavenger in the past 2 years, and only one received multiple refills.

Drugs for UCDs have been studied in small trials for alternative rare inborn errors of metabolism, such as maple syrup urine disease,<sup>17,18</sup> and more common conditions such as hepatic encephalopathy secondary to cirrhosis,<sup>19,20</sup> but do not have additional indications for these conditions. Outpatient prevention of hepatic encephalopathy in the setting of cirrhosis does have other prophylactic alternatives such as rifaximin and lactulose. A combination product of NaPBA-taurursodiol (RELYVRIO) was approved for amyotrophic lateral sclerosis in 2022 but was voluntarily discontinued in 2024 due to lack of efficacy.

A summary of relevant drug information is available in **Appendix 1**, which includes pharmacology and pharmacokinetic characteristics of these drugs, contraindications, warnings and precautions, including any Black Boxed Warnings and Risk Evaluation Mitigation Strategies.

**Table 3. Indications and Dosing.**

Drug Name	Manufacturer	Oral form	Strength	Indication(s)	Dose and Frequency
glycerol phenylbutyrate (RAVICTI) <sup>14</sup>	Horizon (Amgen)	Liquid	1.1 g/mL	Chronic management of patients with urea cycle disorders 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.	The recommended dosage range, based upon body surface area, in patients naïve to phenylbutyrate (PBA) is 4.5 to 11.2 mL/m <sup>2</sup> /day (5 to 12.4 g/m <sup>2</sup> /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 <sup>2</sup> /day

				<p>Safety and efficacy for treatment of N-acetylglutamate synthase (NAGS) deficiency has not been established.</p>	<p>The recommended dosages for patients switching from sodium phenylbutyrate to RAVICTI and patients naïve to phenylbutyric acid are different.</p> <p>For both treatment naïve and experienced patients:</p> <ul style="list-style-type: none"> <li>-Patients 2 years of age and older: Give RAVICTI in 3 equally divided dosages, each rounded up to the nearest 0.5 mL.</li> <li>-Patients less than 2 years: Give RAVICTI in 3 or more equally divided dosages, each rounded up to the nearest 0.1 mL.</li> <li>-Max total daily dosage is 17.5 mL (19 g).</li> <li>-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).</li> </ul>
sodium phenylbutyrate (PHEBURANE) <sup>16</sup>	Medunik USA	Granules	483 mg/g	<p>Adjunctive therapy to standard of care, which includes dietary management, for the chronic management of adult and pediatric patients with urea cycle disorders, involving deficiencies of carbamylphosphate synthetase, ornithine transcarbamylase or argininosuccinic acid synthetase.</p>	<p>The recommended dosage measured as sodium phenylbutyrate is:</p> <p>Patients weighing &lt; 20 kg: 450–600 mg/kg/day of sodium phenylbutyrate orally.</p> <p>Patients weighing ≥ 20 kg: 9.9–13.0 g/m<sup>2</sup>/day of sodium phenylbutyrate orally.</p> <p>Divide the calculated total daily dose into 3 to 6 doses. Administer as 3 to 6 divided doses and take with food. The maximum dosage is 20 grams per day.</p>
sodium phenylbutyrate (OLPRUVA) <sup>21</sup>	Zevra	Pellet pack for suspension	2 g 3 g 4 g 5 g 6 g 6.67 g	<p>Adjunctive therapy to standard of care, which includes dietary management, for the chronic management of adult and pediatric patients weighing 20 kg or greater and with a body surface area of 1.2 m<sup>2</sup> or greater, with urea cycle disorders involving deficiencies of carbamylphosphate synthetase, ornithine transcarbamylase, or argininosuccinic acid synthetase.</p> <p>Combine OLPRUVA with dietary protein restriction and, in some cases, amino</p>	<p>The recommended dosage is 9.9 to 13 g/m<sup>2</sup>/day</p> <p>Max dosage is 20 g/d</p> <p>Administer as 3 to 6 divided doses and take with food.</p>

				acid supplementation (e.g., essential amino acids, arginine, citrulline, and protein-free calorie supplements).	
sodium phenylbutyrate (BUPHENYL, generic) <sup>22</sup>	Horizon (Amgen)	Tablets Powder	500 mg 0.94 g/g	<p>Adjunctive therapy in the chronic management of patients with urea cycle disorders involving deficiencies of carbamoyl phosphate synthetase, ornithine transcarbamylase, or argininosuccinic acid synthetase. It is indicated in all patients with neonatal-onset deficiency (complete enzymatic deficiency, presenting within the first 28 days of life). It is also indicated in patients with late-onset disease (partial enzymatic deficiency, presenting after the first month of life) who have a history of hyperammonemic encephalopathy.</p> <p>Tablets are indicated in children weighing more than 20 kg and adults.</p> <p>BUPHENYL must be combined with dietary protein restriction and, in some cases, essential amino acid supplementation.</p>	<p>450–600 mg/kg/day in patients weighing &lt; 20 kg, 9.9 to 13.0 g/m<sup>2</sup>/day patients 20 kg or more. The tablets and powder are to be taken in equally divided amounts with each meal or feeding (i.e., 3 to 6 times per day).</p> <p>The safety or efficacy of doses in excess of 20 grams (40 tablets) per day has not been established.</p> <p>Pharmacokinetic studies not been conducted in primary patient population (neonates, infants, children) but obtained from normal adult subjects)</p>

**Methods:**

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Canadian Agency for Drugs and Technologies in Health (CADTH), Scottish Intercollegiate Guidelines Network (SIGN), and resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

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**Systematic Reviews:**

After review, 1 systematic review was excluded due to study population (adults with hepatic encephalopathy due to cirrhosis).<sup>20</sup>

**Guidelines:**

High Quality Guidelines: None

**Additional Guidelines for Clinical Context:**

A guideline development group (GDG) of various European physicians, other scientific specialists, and patient group representatives published suggested guidelines for UCD patient care decision making in 2012 using the SIGN evidence levels to score evidence.<sup>11</sup> The literature search details were not well described and these guidelines preceded approval of some currently available nitrogen-scavengers. These guidelines provided detailed information related to acute, inpatient care of hyperammonemia. Long-term care focused on recommendations for: low protein diet, essential amino acid supplementation, vitamin and mineral supplementation, medications to increase excretion of waste nitrogen, caring for special situations and provision of emergency regimen in intercurrent illnesses, and liver transplantation for selected patients.<sup>11</sup>

Discussion of nitrogen scavengers was limited to sodium benzoate (not available in oral dosage form in United States [US]) and the then recently introduced NaPBA. Authors questioned superiority of NaPBA due to concerns for unknown long-term side effects, and noted that NaPBA was associated with menstrual dysfunction/amenorrhea in post pubertal females (~25%), decreased appetite, taste disturbances, and unpleasant odor.<sup>11</sup> NaPBA may also deplete branch chain amino acids and increase risk of endogenous protein catabolism.<sup>11</sup> Both drugs may deplete acetyl-CoA, and NaPBA has been reported to cause low albumin.<sup>11</sup> Hypokalemia is possible, and metabolic acidosis can result from high doses.<sup>11</sup>

The GDG revised the 2012 guidelines in 2019 and changed the methods to score evidence using the grading of recommendations, assessment, development, and evaluation (GRADE) methodology.<sup>7</sup> The GDG included professionals from 9 countries. Specifics of literature search databases and search terms were again omitted. New and more palatable versions of NaPBA and GPB had been introduced by time of publication. They recommend nitrogen-scavengers as a mainstay of therapy in UCD patients with individualized dosing for each patient. (Quality of Evidence: Authors voted 1/11 low, 6/11 moderate, 4/11 high).<sup>7</sup> It was noted that sodium benzoate (not available in oral dosage form in US) is first-line at most European centers, while NaPBA or GPB are used by most patients in the US. No specific recommendations for one product over another were made other than preference for sodium benzoate in pregnancy (Expert Opinion).<sup>7</sup>

After review, 2 guidelines were excluded due to poor quality or lack of applicability.<sup>8,9</sup>

**Randomized Controlled Trials:**

A total of 44 citations were manually reviewed from the initial literature search. After further review, 40 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining 4 citations are summarized in the table below. Full abstracts are included in **Appendix 4**.

**Table 4. Description of Randomized Comparative Clinical Trials.**

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
<p>Smith et al 2013<sup>3</sup> NCT01347073</p> <p>OL, NI, Switch study</p>	<p>1. NaPBA 2. PBA-equimolar GPB</p> <p>Day 1: 24 NH3 measurement on pre-study NaPBA dose Day 2: Switch to GPB Day 10 +/- 4: NH3 measurement on GPB</p>	<p>N=15</p> <p>-Age 29 d to 6 y on NaPBA at least 5 days before Day 1 -N = 4 under 2 y -80% White -mean duration NaPBA 19.3 m -G-tube for NaPBA 20% -10/15 had 1 hyperammonemic crisis in prior 12 m (range 0-7/patient) -Diagnosis: 8 ASL, 3 ASS, 3 OTC, 1 ARG</p>	NH3 <sub>24-hour</sub> AUC	<p>Median NH3<sub>24-hour</sub> AUC (μmol/L*hr)</p> <p>1. 604.96 2. 543.08</p> <p>Mean (SD) NH3<sub>24-hour</sub> AUC (μmol/L*hr)</p> <p>1. 914.43 (630.206) 2. 647.63 (379.944)</p> <p>Ratio of Geometric means of NH3<sub>24-hour</sub> AUC 0.79 95% CI 0.593 to 1.055 Non-inferior</p> <p>AE</p> <p>1. NaPBA NR (pre-existing symptoms such as nausea considered “pre-existing”) 2. GPB 6/15 (40%)-all mild</p> <p>SAE None</p> <p>Discontinuations None</p>	<p>-10 day switch then 12 month long term phase (cross-over only reported in publication) -Diet and supplements stable over 10 day period -Confirmed or clinically suspected UCD on stable dose of NaPBA powder for at least 5 days -Blood draws unable to be performed in 1 patient each dosing NaPBA and GPB -Non-inferiority defined as upper bound of 95% CI ≤ 1.25</p>
<p>Diaz et al 2013<sup>4</sup></p> <p>HPN-100-006 NCT00992459</p> <p>Phase 3, RCT, DB, DD, cross-over in adults</p>	<p>1. NaPBA 2. GPB</p> <p>PBA-equimolar dosing between groups based on patient baseline dose</p> <p>14 days each treatment</p>	<p>N=46 enrolled N=45 received drug N=44 completed study (ITT)</p> <p>-Adults -68.9% Female -Median age 28y -UCD subtype: OTC 88.9%, CPS 4.4%, ASS 6.7% -Race/Ethnicity NR</p>	NH3 <sub>24-hour</sub> AUC	<p>Mean (SD) NH3<sub>24-hour</sub> AUC (μmol/L*hr)</p> <p>1. 976.6 (865.35) 2. 865.9 (660.53)</p> <p>Ratio of Geometric means of NH3<sub>24-hour</sub> AUC 0.91 95% CI 0.799 to 1.034 Non-inferior</p> <p>AE</p> <p>1. 51% 2. 61%</p>	<p>-Computer-generated central randomization -Diet and protein intake stable -Non-inferiority defined as upper bound of 95% CI for ratio of LSM &lt;/= 1.25 -Treatment compliance of 80% was 98% for NaPBA and 100% for GPB doses.</p>



		-Mean duration NaPBA 13 y		Generally mild GI complaints  SAE 1 on GBA (gastroenteritis)  Withdrawals 2 on NaPBA (hyperammonemic crisis and high NH3 with headache)  Deaths none	
Berry et al <sup>1</sup>  HPN100-009 NCT02246218  Phase 4, MC, OL, single-arm	Transition to GPB over 24 h with 24-48 hr ammonia monitoring, optional long-term follow-up until age 2 y or until at least 6 months of treatment and patient able to obtain commercially available product.	N=10 PK study N=9 Long term  - 2 month to < 2 y old -Mean age 9.9 months - 50% Female -Any UCD subtype except NAGS	Successful transition to GPB with controlled NH3 (NH3<100 µmol/L & no clinical symptoms)	Successful Transition 100%  HAC 0.0005/half-year patient exposure  NH3 during GPB transition (see below, results combined with HPN100-12 and HPN100-011)  Before/after HAC (see below, results combined with HPN100-12 and HPN100-011)	-Pooled data only for 2 month – 2 y age range. NCT02246218 included 0-2 month cohort (N=16) and 2 month-2 year cohort (N=10). See Longo et al <sup>2</sup> below for 0-2 month cohort results. -Withdrawal- 2 liver transplant (UCD cure), 1 adverse event, 1 LTFU
Berry et al <sup>1</sup>  HPN100-012(SO) NCT01347073 and HPN100-011 NCT01257737  OL, switch study	10-day switch over NaPBA to GPB	N=4 PK N=7 Long term  - 2 month to < 2 y old -mean age 11.1 months -71.4% Female	Successful transition to GPB with controlled NH3 (NH3<100 µmol/L & no clinical symptoms)	Successful Transition (combined studies with HPN100-009 above, N=17) 16 (94.1%)  NH3 during GPB transition in µmol/L; mean (SD; min-max) (combined studies with HPN100-009 above, N=17) Baseline: 89.2 (63.1; 25.5-287) After: 60.8 (33.4; 23.5-150) Change -28.4, P=0.003 CI NR	Notes apply to combined HPN100-009, HPN100-12, and HPN100-011; 2 month to 2 y age -2 patients discontinued within 2 months for liver transplant (UCD cure), 1 patient withdrew due to SAE of HAC, 1 patient died from sepsis after HAC and surgical complications (bowel perforation and peritonitis) after jejunal tube placement -82% completed 3 months and 53% 6 months of therapy at time of publication

				Before/after switch HAC (combined studies with HPN100-009 above, N=17) Before: 11 patients had 36 HAC pre-GPB After: 7 patients had 11 HAC after GPB	
Longo et al <sup>2</sup> NCT02246218	Transition to GPB over 1-4 days  Safety extension 6 months to 2 y	N=16 received study drug  -Newborn to < 2 month old -Median age: 0.48 months old -56.3% Male -Treatment naïve or experienced with NaPBA or IV NA phenylacetate/Na benzoate -UCD all types except NAGS	Successful transition to GPB with controlled NH3 (NH3<100 µmol/L & no clinical symptoms)	Successful Transition 100% Baseline NH3: 94.3 µmol/L End of transition NH3: 50.4 µmol/L  Before/after GPB HAC Before: 6 of 16 patients had 1 HAC and 1 patient had 2 HAC After: 3 of 16 patients had 1 HAC and 2 patients had 2 HAC and 5 had NH3 >100 µmol/L  TEAE primarily GI related	-4 withdrawn for liver transplant (UCD cure), 1 withdrawn by parent, 1 discontinued due to AE (elevated liver enzymes) -88.2% completed at least 1 month, 58.8% completed at least 3 months, 17.6% completed at least 6 months.

Abbreviations: AE=adverse event; ASL=argininosuccinate lyase deficiency, ASS=argininosuccinic acid synthetase deficiency, ARG=arginase deficiency, CI=confidence interval; CPS=carbamoyl phosphate synthetase deficiency; d=day, DB=double-blind; DD=double-dummy; GBA=glycerol phenylbutyrate; GI=gastrointestinal; HAC=hyperammonemic crisis; ITT=intention-to-treat; IV=intravenous; LSM=least squares mean; LTFU=lost to follow up; m=month; MC=multi-center; NAGS=N-acetyl glutamate synthetase deficiency; NaPBA=sodium phenylbutyrate, NH3=ammonia; NH3<sub>24-hour AUC</sub> = ammonia 24-hour area under the curve; NR = not reported; OL=open-label; OTC=ornithine transcarbamylase deficiency, PBA=phenylbutyrate; PK=pharmacokinetic; RCT=randomized controlled trial; SAE=serious adverse event; SD=standard deviation; UCD=urea cycle disorder, y=year

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**Appendix 1: Specific Drug Information\***

Generic	Brand	Route	Form	PDL
glycerol phenylbutyrate	RAVICTI	ORAL	LIQUID	
sodium phenylbutyrate	PHEBURANE	ORAL	GRANULES	
sodium phenylbutyrate	OLPRUVA	ORAL	PELET PACK	
sodium phenylbutyrate	BUPHENYL	ORAL	POWDER	
sodium phenylbutyrate	SODIUM PHENYLBUTYRATE	ORAL	POWDER	
sodium phenylbutyrate	BUPHENYL	ORAL	TABLET	
sodium phenylbutyrate	SODIUM PHENYLBUTYRATE	ORAL	TABLET	

\*CARBAGLU (carglumic acid, dispersible table) assigned to orphan drug policy and PA

**Table 5. Clinical Pharmacology and Pharmacokinetics.**

Drug Name	Mechanism of Action	Absorption	Metabolism/Excretion	Pharmacokinetics (mean)
glycerol phenylbutyrate (RAVICTI) <sup>14</sup> Liquid	Triglyceride containing 3 molecules of phenylbutyrate which are released from glycerol backbone in gastrointestinal tract by pancreatic lipases. Phenylbutyrate then oxidized to phenylacetate, the active moiety of RAVICTI. Phenylacetate conjugates with glutamine (which contains 2 molecules of nitrogen) via acetylation in the liver and kidneys to form phenylacetylglutamine, which is excreted by the kidneys.	<ul style="list-style-type: none"> <li>Tmax: 8 hours PBA; 12 hours PAA; 10 hours PAGN</li> <li>Cmax: 66 mcg/mL PBA, 28 mcg/mL PAA, 4mL TID dose</li> <li>AUC: 930 mcg•hr/mL PBA, 942 mcg•hr/mL PAA, 4mL TID dose</li> </ul>	<p>Gastrointestinal tract: extensive by pancreatic lipase hydrolysis Liver: extent not specified Kidney: extent not specified</p> <p>PBA (major): inactive PAA: active PAGN: inactive inhibitor of CYP2C9, CYP2D6, CYP3A4/5, CYP1A2, CYP2C8, CYP2C19, and CYP2D6</p> <p>Excretion as PAGN Renal: 68.9% (adult), 66.4% (pediatric)</p>	<ul style="list-style-type: none"> <li>Protein binding, PBA: 80.6% to 98%</li> <li>Protein binding, PAA: 37.1% to 65.6%</li> <li>Protein binding, PAGN: 7% to 12%</li> </ul>
sodium phenylbutyrate (PHEBURANE) <sup>16</sup> Granules	Pro-drug is metabolized to phenylacetate. Phenylacetate is a metabolically active compound that conjugates with glutamine via acetylation to form phenylacetylglutamine.	<ul style="list-style-type: none"> <li>Cmax: 146-169 mcg/mL, decreased 43-55% with food</li> <li>AUC: 272-283 mcg•hr/mL, decreased 40-63% with food</li> </ul>	<ul style="list-style-type: none"> <li>Half-life: 0.5-0.8 hours</li> <li>80–100% of sodium PBA is excreted by the kidneys within 24 hours as PAGN.</li> </ul>	NR
sodium phenylbutyrate (OLPRUVA) <sup>21</sup> Pellet pack for suspension	Phenylacetylglutamine is excreted by the kidneys and provides	<ul style="list-style-type: none"> <li>Cmax: 229 mcg/mL decreased 50% with food</li> </ul>	<ul style="list-style-type: none"> <li>Half-life: 0.5 hours</li> </ul>	<ul style="list-style-type: none"> <li>Vd 7.2L</li> </ul>

	mechanism for waste nitrogen excretion.	<ul style="list-style-type: none"> <li>AUC: 510 mcg•hr/mL, decreased 39% with food</li> </ul>	<ul style="list-style-type: none"> <li>80–100% of sodium phenylbutyrate is excreted by the kidneys within 24 hours as PAGN.</li> </ul>	
sodium phenylbutyrate (BUPHENYL, generic) <sup>22</sup> Tablets Powder		Cmax: 218 mcg/mL tablet, 195 mcg/mL powder Effect of food unknown	<ul style="list-style-type: none"> <li>Half-life: 0.76-0.77 hours</li> <li>80–100% of sodium PBA is excreted by the kidneys within 24 hours as PAGN.</li> </ul>	NR
Abbreviations: AUC=area under the curve; Cmax=maximum concentration; NR=not reported; PAA=phenylacetate; PAGN=phenylacetylglutamine; PBA=phenylbutyrate; TID=three times daily; Tmax=time to maximum concentration; Vd=volume of distribution.				

**Drug Safety:**

Boxed Warnings: None

Risk Evaluation Mitigation Strategy Programs: None

**Contraindications:**

- Should not be used in managing acute hyperammonemia, a medical emergency. (BUPHENYL)<sup>22</sup>
- Known hypersensitivity to phenylbutyrate

**Table 6. Summary of Warnings and Precautions.**

<b>Warning/Precaution</b>	glycerol phenylbutyrate (RAVICTI) <sup>14</sup>	sodium phenylbutyrate (PHEBURANE) <sup>16</sup>	sodium phenylbutyrate (OLPRUVA) <sup>21</sup>	sodium phenylbutyrate (BUPHENYL, generic) <sup>22</sup>
Hypersensitivity to active ingredient or any component of preparation	X			X
Use in heart failure, severe renal insufficiency and clinical states with sodium retention and edema		X	X	X
Use in renal insufficiency, hepatic insufficiency, or inborn errors of beta oxidation.				X
Use with probenecid	X	X	X	X
Use of corticosteroids, haloperidol, or valproic acid	X	X	X	X
Neurotoxicity of phenylacetate	X	X	X	
Hypokalemia		X	X	
Diabetes mellitus, hereditary fructose intolerance, glucose-galactose malabsorption, or sucrase-isomaltase insufficiency		X		
Pancreatic Insufficiency or Intestinal malabsorption	X			

## Appendix 2: Medline Search Strategy

**Database:** Ovid MEDLINE(R) ALL <1946 to October 04, 2024>

#	Query	Results from 8 Oct 2024
1	glycerol phenylbutyrate.mp.	72
2	sodium phenylbutyrate.mp.	277
3	Ravicti.mp.	8
4	pheburane.mp.	7
5	Buphenyl.mp.	10
6	1 or 2 or 3 or 4 or 5	328
7	limit 6 to (english language and humans and yr="1990 -Current")	228
8	limit 7 to (adaptive clinical trial or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or comparative study or equivalence trial or guideline or meta analysis or multicenter study or practice guideline or randomized controlled trial)	43
9	Urea Cycle Disorders, Inborn/dh, dt, th [Diet Therapy, Drug Therapy, Therapy]	138
10	limit 9 to (english language and humans)	131
11	limit 10 to (yr="1990 -Current" and (adaptive clinical trial or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or comparative study or controlled clinical trial or equivalence trial or guideline or meta analysis or multicenter study or practice guideline or randomized controlled trial or "review" or "systematic review"))	58

- Results from cochranelibrary.com manually searched (Accessed: Oct 4, 2024).  
Keywords: glycerol phenylbutyrate, sodium phenylbutyrate, urea cycle disorders
- Publications from Urea Cycle Disorders Consortium (<https://ucdc.rarediseasesnetwork.org/research-publications>) manually searched 2003-2024 (Accessed 10/12/2024).

### Appendix 3: Key Inclusion Criteria

<b>Population</b>	People with urea cycle disorders
<b>Intervention</b>	Glycerol phenylbutyrate, sodium phenylbutyrate
<b>Comparator</b>	Glycerol phenylbutyrate, sodium phenylbutyrate
<b>Outcomes</b>	Ammonia levels, hyperammonemic crisis, mortality
<b>Timing</b>	Any
<b>Setting</b>	Outpatient

### Appendix 4: Abstracts

Ammonia Control in Children Ages 2 Months through 5 Years with Urea Cycle Disorders: Comparison of Sodium Phenylbutyrate and Glycerol Phenylbutyrate  
W Smith, MD, GA Diaz, MD, PhD, U Lichter-Konecki, MD, PhD, SA Berry, MD, CO Harding, MD, SE McCandless, MD, C LeMons, J Mauney, MS, K Dickinson, DF Coakley, PharmD, TL Moors, MS, M Mokhtarani, MD, M Mokhtarani, MD, BF Scharschmidt, MD, and B Lee, MD, PhD  
J Pediatr. 2013 June ; 162(6): 1228–1234.e1. doi:10.1016/j.jpeds.2012.11.084.

**Objectives**—To examine ammonia levels, pharmacokinetics (PK), and safety of glycerol phenylbutyrate (GPB, HPN-100) and sodium phenylbutyrate (NaPBA) in young children with urea cycle disorders (UCDs).

**Study design**—This open label switch-over study enrolled patients ages 29 days to under 6 years taking NaPBA. Patients underwent 24-hr blood and urine sampling on NaPBA and again on a PBA-equimolar dose of GPB and completed questionnaires regarding signs and symptoms associated with NaPBA and/or their UCD.

**Results**—15 patients (8 ASL, 3 ASS, 3 OTC, 1 ARG) ages 2 months through 5 years enrolled in and completed the study. Daily ammonia exposure (24-hour AUC) was lower on GPB and met predefined non-inferiority criteria (ratio of means 0.79; 95% CI 0.593–1.055;  $p = 0.03$  Wilcoxon; 0.07 t-test). Six patients experienced mild AEs on GPB; there were no SAEs or significant lab changes. Liver tests and ASA levels among patients with ASL were unchanged or improved on GPB. Eleven of 15 patients reported 35 symptoms on Day 1; 23 of these 35 symptoms improved or resolved on GPB. Mean systemic exposure to PBA, PAA and PAGN were similar and PAA exposure tended to be higher in the youngest children on both drugs. Urinary PAGN concentration was greater on morning voids and varied less over 24 hours on GPB versus NaPBA.

**Conclusions**—GPB results in more evenly distributed urinary output of PAGN over 24 hours, was associated with fewer symptoms and offers ammonia control comparable with that observed with NaPBA in young children with UCDs.

### AMMONIA CONTROL AND NEUROCOGNITIVE OUTCOME AMONG UREA CYCLE DISORDER PATIENTS TREATED WITH GLYCEROL PHENYLBUTYRATE

George A. Diaz, Lauren S. Krivitzky, Masoud Mokhtarani, William Rhead, James Bartley, Annette Feigenbaum, Nicola Longo, William Berquist, Susan A. Berry, Renata Gallagher, Uta Lichter-Konecki, Dennis Bartholomew, Cary O. Harding, Stephen Cederbaum, Shawn E. McCandless, Wendy Smith, Gerald Vockley, Stephen A. Bart, Mark S. Korson, David Kronn, Roberto Zori, J. Lawrence Merritt II, Sandesh Sreenath-Nagamani, Joseph Mauney, Cynthia LeMons, Klara Dickinson, Tristen L. Moors, Dion F. Coakley, Bruce F. Scharschmidt, and Brendan Lee  
Hepatology. 2013 June ; 57(6): 2171–2179. doi:10.1002/hep.26058.

**Background**—Glycerol phenylbutyrate is under development for treatment of urea cycle disorders (UCDs), rare inherited metabolic disorders manifested by hyperammonemia and neurological impairment.



**Methods**—We report the results of a pivotal phase 3, randomized, double-blind, crossover trial comparing ammonia control, assessed as 24-hour area under the curve (NH<sub>3</sub>-AUC<sub>0-24hr</sub>), and pharmacokinetics during treatment with glycerol phenylbutyrate versus sodium phenylbutyrate (NaPBA) in adult UCD patients and the combined results of 4 studies involving short- and long-term glycerol phenylbutyrate treatment of UCD patients ages 6 and above. **Results**—Glycerol phenylbutyrate was non-inferior to NaPBA with respect to ammonia control in the pivotal study, with mean (SD) NH<sub>3</sub>-AUC<sub>0-24hr</sub> of 866 (661) versus 977 (865) μmol·h/L for glycerol phenylbutyrate and NaPBA, respectively. Among 65 adult and pediatric patients completing 3 similarly designed short term comparisons of glycerol phenylbutyrate versus NaPBA, NH<sub>3</sub>-AUC<sub>0-24hr</sub> was directionally lower on glycerol phenylbutyrate in each study, similar among all subgroups, and significantly lower (p<0.05) in the pooled analysis, as was plasma glutamine. The 24-hour ammonia profiles were consistent with slow release behavior of glycerol phenylbutyrate and better overnight ammonia control. During 12 months of open label glycerol phenylbutyrate treatment, average ammonia was normal in adult and pediatric patients and executive function among pediatric patients, including behavioral regulation, goal setting, planning and self-monitoring, was significantly improved. **Conclusions**—Glycerol phenylbutyrate exhibits favorable pharmacokinetics and ammonia control relative to NaPBA in UCD patients, and long-term glycerol phenylbutyrate treatment in pediatric patients was associated with improved executive function (ClinicalTrials.gov NCT00551200, NCT00947544, NCT00992459, NCT00947297).

Safety and efficacy of glycerol phenylbutyrate for management of urea cycle disorders in patients aged 2 months to 2 years

Susan A. Berry, Nicola Longo, George A. Diaz, Shawn E. McCandless, Wendy E. Smith, Cary O. Harding, Roberto Zori, Can Ficioglu, Uta Lichter-Konecki, Beth Robinson, Jerry Vockley

Molecular Genetics and Metabolism 122 (2017) 46–53

**Introduction:** Glycerol phenylbutyrate (GPB) is approved in the US for the management of patients 2 months of age and older with urea cycle disorders (UCDs) that cannot be managed with protein restriction and/or amino acid supplementation alone. Limited data exist on the use of nitrogen conjugation agents in very young patients.

**Methods:** Seventeen patients (15 previously on other nitrogen scavengers) with all types of UCDs aged 2 months to 2 years were switched to, or started, GPB. Retrospective data up to 12 months pre-switch and prospective data during initiation of therapy were used as baseline measures. The primary efficacy endpoint of the integrated analysis was the successful transition to GPB with controlled ammonia (< 100 μmol/L and no clinical symptoms). Secondary endpoints included glutamine and levels of other amino acids. Safety endpoints included adverse events, hyperammonemic crises (HACs), and growth and development.

**Results:** 82% and 53% of patients completed 3 and 6 months of therapy, respectively (mean 8.85 months, range 6 days–18.4 months). Patients transitioned to GPB maintained excellent control of ammonia and glutamine levels. There were 36 HACs in 11 patients before GPB and 11 in 7 patients while on GPB, with a reduction from 2.98 to 0.88 episodes per year. Adverse events occurring in at least 10% of patients while on GPB were neutropenia, vomiting, diarrhea, pyrexia, hypophagia, cough, nasal congestion, rhinorrhea, rash/papule.

**Conclusion:** GPB was safe and effective in UCD patients aged 2 months to 2 years. GPB use was associated with good short- and long-term control of ammonia and glutamine levels, and the annualized frequency of hyperammonemic crises was lower during the study than before the study. There was no evidence for any previously unknown toxicity of GPB.

Glycerol phenylbutyrate efficacy and safety from an open label study in pediatric patients under 2 months of age with urea cycle disorders

Nicola Longo, George A. Diaz, Uta Lichter-Konecki, Andreas Schulz, Michal Inbar-Feigenberg, Robert L. Conway, Allison A. Bannick, Shawn E. McCandless, Roberto Zori, Bryan Hainline, Nicholas Ah Mew, Colleen Canavan, Thomas Vescio, Teresa Kok, Marty H. Porter, Susan A. Berry

Molecular Genetics and Metabolism 132 (2021) 19–26

Author: Fletcher

December 2024

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**Background/Aims:** Neonatal onset Urea cycle disorders (UCDs) can be life threatening with severe hyperammonemia and poor neurological outcomes. Glycerol phenylbutyrate (GPB) is safe and effective in reducing ammonia levels in patients with UCD above 2 months of age. This study assesses safety, ammonia control and pharmacokinetics (PK) of GPB in UCD patients below 2 months of age.

**Methods:** This was an open-label study in UCD patients aged 0 – 2 months, consisting of an initiation/transition period (1 – 4 days) to GPB, followed by a safety extension period (6 months to 2 years). Patients presenting with a hyperammonemic crisis (HAC) did not initiate GPB until blood ammonia levels decreased to below 100  $\mu\text{mol/L}$  while receiving sodium phenylacetate/sodium benzoate and/or hemodialysis. Ammonia levels, PK analytes and safety were evaluated during transition and monthly during the safety extension for 6 months and every 3 months thereafter.

**Results:** All 16 patients with UCD (median age 0.48 months, range 0.1 to 2.0 months) successfully transitioned to GPB within 3 days. Average plasma ammonia level excluding HAC was 94.3  $\mu\text{mol/L}$  at baseline and 50.4  $\mu\text{mol/L}$  at the end of the transition period ( $p= 0.21$ ). No patient had a HAC during the transition period. During the safety extension, the majority of patients had controlled ammonia levels, with mean plasma ammonia levels lower during GPB treatment than baseline. Mean glutamine levels remained within normal limits throughout the study. PK analyses indicate that UCD patients <2 months are able to hydrolyze GPB with subsequent absorption of phenylbutyric acid (PBA), metabolism to phenylacetic acid (PAA) and conjugation with glutamine. Plasma concentrations of PBA, PAA, and phenylacetylglutamine (PAGN) were stable during the safety extension phase and mean plasma phenylacetic acid: phenylacetylglutamine ratio remained below 2.5 suggesting no accumulation of GPB. All patients reported at least 1 treatment emergent adverse event with gastroesophageal reflux disease, vomiting, hyperammonemia, diaper dermatitis (37.5% each), diarrhea, upper respiratory tract infection and rash (31.3% each) being the most frequently reported.

**Conclusions:** This study supports safety and efficacy of GPB in UCD patients aged 0 -2 months who cannot be managed by dietary protein restriction and/or amino acid supplementation alone. GPB undergoes intestinal hydrolysis with no accumulation in this population.