



Urea Cycle Disorders Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
carglumic acid (Carbaglu®) ¹	generic, Orphan Europe/Recordati Rare Diseases	<ul style="list-style-type: none"> Adjunctive therapy for the treatment of acute hyperammonemia due to the deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS) Maintenance therapy for the treatment of chronic hyperammonemia due to the deficiency of the hepatic enzyme NAGS Adjunctive therapy to standard of care for the treatment of acute hyperammonemia due to propionic acidemia (PA) or methylmalonic acidemia (MMA)
glycerol phenylbutyrate (Ravicti®)* ²	Horizon	<ul style="list-style-type: none"> Chronic management of patients with urea cycle disorders (UCDs) who cannot be managed by dietary protein restriction and/or amino acid supplementation alone; must be used with dietary protein restriction and, in some cases, dietary supplements (e.g., essential amino acids, arginine, citrulline, protein-free calorie supplements)[†]
sodium phenylbutyrate (Buphenyl®) ³	generic, Horizon	<ul style="list-style-type: none"> Adjunctive therapy in the chronic management of patients with UCDs (either neonatal-onset or late-onset disease) involving deficiencies of carbamyl phosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid synthetase (AS); must be combined with dietary protein restriction and, in some cases, essential amino acid supplementation
sodium phenylbutyrate (Pheburane)* ⁴	Medunik	<ul style="list-style-type: none"> Adjunctive therapy to standard of care, which includes dietary management, for the chronic management of adult and pediatric patients with urea cycle disorders (UCDs), involving deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC) or argininosuccinic acid synthetase (AS); use in combination with dietary protein restriction and, in some cases, essential amino acid supplementation[‡]

*Approved as a New Drug Application (NDA) via the 505(b)(2) pathway. A 505(b)(2) NDA is a Food and Drug Administration (FDA) approval pathway in which at least some of the information required for approval comes from studies not conducted by or for the applicant.^{5,6}

† Limitations of use: not indicated for treatment of acute hyperammonemia in patients with UCDs; safety and efficacy for treatment of NAGS deficiency have not been established.

‡ Limitations of use: not indicated for the treatment of acute hyperammonemia, a life-threatening medical emergency that requires rapid interventions to decrease plasma ammonia levels.

OVERVIEW

Urea cycle disorders (UCDs) are inherited deficiencies of enzymes or transporters that function in the synthesis of urea from ammonia within the body. The urea cycle maintains low levels of ammonia that would otherwise accumulate in the blood due to protein breakdown.⁷ The purpose of the urea cycle, which converts 2 moles of nitrogen (1 from ammonia, 1 from aspartate) to urea, is to transform nitrogen into a water soluble form that may be excreted.^{8,9} UCDs are most often related to the first 4 enzymes within the cycle: carbamyl phosphate synthetase (CPS), ornithine transcarbamylase (OTC), argininosuccinate synthetase (AS), and argininosuccinate lyase (ASL). They may also result from a deficiency in N-acetylglutamate synthetase (NAGS), the enzyme for the cofactor in N-acetylglutamate production. Arginase deficiency also affects urea production as arginase is required in the last step of urea production.

In the United States (US), the combined incidence of the multiple types of UCDs is estimated to be approximately 1 per 20,000 to 25,000 live births; however, some estimate it is much more frequent (1 per 8,000) internationally.¹⁰ Most UCDs affect males and females equally. Cases may be inherited or acquired. Those presenting as newborns often develop symptoms within 24 to 48 hours following birth. Presentation at birth or childhood is most common; however, UCDs may occur later in life. Diagnosis relies on recognition of the elevated ammonia level, further evaluation, amino acid and/or tissue enzyme analysis, and ultimately genetic testing. Testing for UCDs is now included in many newborn screening programs. The UCD consortium consists of 14 sites in the US, Canada, and Europe, and population data have been published as a result of research from these sites.^{11,12,13} Subtypes of UCDs are listed below.

- OTC deficiency is an X-linked disorder.¹⁴ Notably, its clinical onset is unpredictable and is generally after childhood in otherwise normal individuals. It has a US incidence rate of approximately 1 in 20,000 to 80,000 live births. In older individuals, the initial onset may occur at ages 40 to 50 years or older. Morbidity and mortality are high, particularly in patients with the neonatal form of OTC deficiency. As this is an X-linked disorder, it predominantly affects males.
- ASL deficiency affects approximately 1 per 70,000 live births and is the second-most common UCD.¹⁵ The autosomal recessive disorder may manifest in either infancy or later in life. Like most UCDs, morbidity and mortality with this disorder are high. Select populations around the world have been found to have a much higher incidence compared to the general population (e.g., Druze community in Israel).
- Argininosuccinate synthetase (AS) deficiency, also known as citrullinemia I, is an autosomal recessive disorder as well.¹⁶ True incidence is unknown but is estimated to be approximately 1 per 250,000 live births in the US. Morbidity and mortality are high.
- CPS deficiency is an autosomal recessive disorder.¹⁷ Due to its rarity, the incidence is unknown. If untreated, the deficiency is likely fatal; it may occur in patients of all ages. Often, symptoms may be gradual in onset, including gradual resulting brain damage. In newborns, rapid demise often occurs without immediate recognition and treatment.
- NAGS deficiency may be mistaken for CPS deficiency and is thought to be very rare; its true incidence is also unknown.¹⁸ Like most UCDs, it is inherited as an autosomal recessive trait. Presentation may occur at any age but is most likely during the newborn period. As with most UCDs, morbidity and mortality are high.
- Arginase deficiency, which is also an autosomal recessive disorder, is one of the least common types of UCDs.¹⁹ Progression is often relatively slow in comparison with other UCDs, and spasticity occurs more frequently with this disorder. Morbidity is high, but mortality appears infrequently as hyperammonemia is less common and typically not severe; however, the true estimate of mortality may be underrepresented due to lack of reliable statistics measuring outcomes in this population.
- Citrin deficiency, also known as citrullinemia II, another autosomal recessive disorder, may also result in hyperammonemia.²⁰ It may present in infancy but is most likely to present with insidious onset in adulthood.
- Ornithine translocase deficiency, also known as HHH syndrome (hyperornithinemia, hyperammonemia, homocitrullinuria), is similar to UCDs and is often grouped with UCDs. It leads to high plasma ornithine concentrations, ultimately causing impaired ureagenesis.²¹ Hyperammonemia may be intermittent, but growth and intellectual development are still affected.

The inability to synthesize urea due to a UCD leads to accumulation of ammonia in the blood, or hyperammonemia.²² Signs and symptoms of early-onset, or infant, hyperammonemia include lethargy, irritability, poor feeding, vomiting, hyperventilation, and seizures.²³ Signs and symptoms of late-onset (later in life) hyperammonemia include intermittent ataxia, impaired cognition, failure to thrive, gait abnormalities, seizures, headaches, and vomiting. In general, the risk of hyperammonemia is associated with its neurotoxicity; however, the mechanism by which elevated ammonia levels in the central nervous system (CNS) causes brain damage is not fully determined.²⁴ High ammonia levels in the CNS may alter other important compounds, transporter molecules, and/or neurotransmission. In addition, cerebral edema may occur.

While patients with UCDs may experience hyperammonemia solely as a result of the disorder, other stressors may affect the urea cycle function.²⁵ These include liver damage, toxins, infections, drugs (e.g., valproic acid, chemotherapy, antifungals, acetaminophen), other metabolic diseases, and nitrogen overload (e.g., post-partum stress, gastrointestinal bleeding, hemolysis, protein catabolism).

Hyperammonemia should be treated as an emergency.^{26,27} In acute situations, nitrogen intake (e.g., protein) should be stopped, and the patient should be hydrated to maintain good urine output. If needed, parenteral intake of calories from glucose and lipids should be used. Dialysis, with hemodialysis preferred, may be used to acutely remove ammonia from the blood. Intravenous (IV) sodium benzoate/sodium phenylacetate (Ammonul®) may be used in acute situations to further reduce ammonia levels.²⁸ This product functions similarly to 2 of the oral agents within this class; it acts as a nitrogen scavenger to provide an alternative method of nitrogen excretion. Hydration via intravenous fluids may be sufficient to treat mild hyperammonemia. Supplemental arginine and/or citrulline may also be used in treatment. Carglumic acid (Carbaglu) may also be used for the acute treatment of hyperammonemia in patients with NAGS deficiency.

The 2019 trans-European suggested guidelines for the diagnosis and management of urea cycle disorders address all products for acute hyperammonemia.²⁹ Intravenous sodium benzoate/sodium phenylacetate is indicated for any UCD in this setting. Carglumic acid is recommended to treat acute hyperammonemia in patients with for NAGS deficiency and in patients without a UCD diagnosis in combination with other treatments. Once stabilized, maintenance therapy with an agent within this class, when appropriate, may be initiated. The suggested guidelines recommend nitrogen scavengers (e.g., sodium phenylbutyrate, glycerol phenylbutyrate) at individualized doses to improve metabolic stability in the long term. Dividing the dose and administering with ample fluids limits mucositis or gastritis associated with phenylbutyrate products. Carglumic acid is recommended first-line for the treatment of NAGS deficiency. In addition, protein restriction while maintaining an adequate supply needed for growth is fundamental to treatment of these disorders. Select patients with UCDs are also candidates for liver transplant.

Prior to the US Food and Drug Administration (FDA) approval of agents in this class, most patients were treated symptomatically. This therapeutic class review focuses on the role of these agents in the maintenance treatment of UCDs.

PHARMACOLOGY^{30,31,32,33}

Carglumic acid (Carbaglu) is a synthetic structural analogue of endogenous N-acetylglutamate (NAG), which is produced by NAGS and serves as a carbamoyl phosphate synthetase 1 (CPS 1) activator in liver mitochondria. CPS 1 is the first enzyme needed in the pathway to convert ammonia to urea (urea cycle).

Glycerol phenylbutyrate (Ravicti) is a triglyceride containing 3 molecules of phenylbutyrate, and its metabolite, phenylacetate (PAA), is the active component. Similarly, sodium phenylbutyrate (Buphenyl, **Pheburane**) is converted to PAA, its active form. PAA conjugates with glutamine, containing 2 nitrogen molecules, via liver and kidney acetylation to form phenylacetylglutamine (PAGN), which is subsequently excreted by the kidneys. Thus, glycerol phenylbutyrate and sodium phenylbutyrate provide an alternate pathway for excretion of nitrogen.

PHARMACOKINETICS^{34,35,36,37}

Drug	Tmax (hr)	Metabolism	Half-Life (hr)	Excretion (%)
carglumic acid (Carbaglu)	3 (range, 2–4)	metabolized by intestinal bacterial flora (likely to carbon dioxide)	5.6 (range 4.3–9.5)	urine: 9 feces: 60
glycerol phenylbutyrate (Ravicti)	phenylbutyrate, 2 PAA, 4 PAGN, 4	pancreatic lipases convert to phenylbutyrate, which is oxidized to PAA; PAGN formed by PAA and glutamine conjugation	nd	nd
sodium phenylbutyrate (Buphenyl)	phenylbutyrate, 1 PAA, 3.55 (both fasting)	metabolized to PAA; PAGN formed by PAA and glutamine conjugation	phenylbutyrate, 0.76 PAA, 1.29	urine: 80–100
sodium phenylbutyrate (Pheburane)	phenylbutyrate, 0.6 (fasting)	metabolized to PAA; PAGN formed by PAA and glutamine conjugation	phenylbutyrate, 0.5–0.8	urine: 80–100

nd = no data; Tmax = time to maximum serum concentration

CONTRAINDICATIONS/WARNINGS^{38,39,40,41}

Contraindications

Carglumic acid (Carbaglu) has no contraindications.

Glycerol phenylbutyrate (Ravicti) is contraindicated in patients with known hypersensitivity to phenylbutyrate.

Sodium phenylbutyrate (Buphenyl, **Pheburane**) should not be used for the treatment of acute hyperammonemia, which should be managed as a medical emergency.

Warnings

carglumic acid (Carbaglu)

Acute symptomatic hyperammonemia should be treated as an emergency and may require dialysis and/or hemofiltration to remove ammonia to prevent any brain injury or damage or death. Management of cases due to NAGS should be in conjunction with healthcare providers experienced in the treatment of metabolic disorders. Routinely measure plasma ammonia levels, neurological status, clinical response, and laboratory results to assess carglumic acid response. Maintain normal plasma ammonia levels by adjusting the dose based on patient response. In cases of hyperammonemia, completely restrict protein for no longer than 12 to 36 hours while maximizing caloric supplementation to reverse catabolism and nitrogen turnover. Following improvement, protein should be introduced as early as possible. Ongoing

monitoring of ammonia levels, neurological status, growth, protein/nutritional status, and relevant laboratory tests should be part of evaluation to treatment.

glycerol phenylbutyrate (Ravicti) and sodium phenylbutyrate (Buphenyl, Pheburane)

The major metabolite of glycerol phenylbutyrate and sodium phenylbutyrate, PAA, may cause neurotoxicity, including somnolence, fatigue, headache, lightheadedness, dysgeusia, disorientation, hypoacusis, memory impairment, and exacerbation of preexisting neuropathy.

Low or absent pancreatic enzymes or intestinal disease leading to fat malabsorption may lead to reduced control or plasma ammonia via reduced or absent metabolism of glycerol phenylbutyrate and absorption of phenylbutyrate. Ammonia levels in these populations should be monitored closely.

Sodium phenylbutyrate should not be used in patients with known hypersensitivity to phenylbutyrate or another component.

Monitor serum potassium levels in patients taking sodium phenylbutyrate oral pellets (Pheburane) since renal excretion of the metabolite may lead to urinary potassium loss.

Use sodium phenylbutyrate cautiously in patients with congestive heart failure, severe renal insufficiency, and in patients with sodium retention and edema. **Discontinue sodium phenylbutyrate oral pellets (Pheburane) and institute appropriate therapy if new onset or worsening edema develops.** It should also be used cautiously in patients with hepatic or renal insufficiency or inborn errors of beta oxidation as it is metabolized in the liver and kidney.

Sodium phenylbutyrate oral pellets (Pheburane) contain 768 mg of sucrose per gram of sodium phenylbutyrate, which should be considered when prescribing in patients with diabetes mellitus. Avoid use in patients with rare hereditary conditions of fructose intolerance, glucose-galactose malabsorption, or sucrase-isomaltase insufficiency.

DRUG INTERACTIONS^{42,43,44,45}

No drug interaction studies have been performed with carglumic acid (Carbaglu). Based on *in vitro* data, it is not an inducer of cytochrome P450 (CYP) 1A1/2, CYP2B6, CYP2C, and CYP3A4/5 enzymes or an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5 enzymes.

Glycerol phenylbutyrate (Ravicti) is a weak inducer of CYP3A4; thus, concomitant use with drugs that are substrates of CYP3A4 may result in decreased efficacy of the concurrent drug, particularly in those with a narrow therapeutic window (e.g., alfentanil, quinidine, cyclosporine). Concomitant use of glycerol phenylbutyrate with midazolam may reduce the efficacy of midazolam. Excretion of glycerol phenylbutyrate's metabolites (e.g., PAGN, PAA) may be reduced by probenecid.

Probenecid may inhibit renal excretion of glycerol phenylbutyrate and sodium phenylbutyrate (Buphenyl, Pheburane) and their metabolites, PAA and PAGN. Patients should be monitored for neurotoxicity and plasma PAA and PAGN levels should be assessed when used concurrently with probenecid.

Use of corticosteroids may lead to increased protein breakdown and, subsequently, increased ammonia levels. Likewise, hyperammonemia has been reported with haloperidol and valproic acid. Closely monitor ammonia levels in patients using these drugs concomitantly.

ADVERSE EFFECTS^{46,47,48,49}

Drug	Anemia	Abdominal Pain	Diarrhea	Vomiting	Decreased Appetite	Fatigue	Headache	Rash
carglumic acid (Carbaglu)	13	17	13	26	9	nr	13	9
glycerol phenylbutyrate (Ravicti)	≥ 10	7 to ≥ 10	16	7 to ≥ 10	7 to ≥ 10	7 to ≥ 10	14	≥ 10
sodium phenylbutyrate (Buphenyl)	9	2	nr	2	4	reported	< 2	< 2
sodium phenylbutyrate (Pheburane)	< 3	< 3	nr	< 3	≥ 3	reported	< 3	< 3

nr = not reported

Adverse effects are reported as a percentage. Adverse effects data obtained are from the prescribing information and are not meant to be comparative or all inclusive.

The most common adverse reactions (≥ 13%) reported with carglumic acid in a retrospective case series not listed above included infections (9% to 17%), tonsillitis (17%), nasopharyngitis (13%), decreased hemoglobin (13%), and pyrexia (17%). Hyperhidrosis, somnolence, decreased weight, and asthenia were reported in 9% of patients using carglumic acid for NAGS deficiency. When used to treat PA and MMA, the most common adverse reactions (5%) included; neutropenia, anemia, electrolyte imbalances, lethargy, and decreased appetite.

The most common adverse reactions in adult patients (≥ 10%) reported with glycerol phenylbutyrate not described above were nausea and dizziness. The most common adverse reaction in pediatric patients 2 years of age and older (≥ 10%) reported with glycerol phenylbutyrate not described above was nausea. In patients ages 2 months to < 2 years, adverse reactions occurring in ≥ 10% of patients and not listed in the above table are neutropenia, pyrexia, constipation, hypophagia, cough, nasal congestion, rhinorrhea, and papule. The most common adverse reactions in pediatric patients < 2 months of age (≥ 10%) experienced in a clinical trial and not reported above were vomiting, rash, gastroesophageal reflux, increased hepatic enzymes, feeding disorder (decreased appetite, hypophagia), cough, dehydration, metabolic acidosis, thrombocytosis, thrombocytopenia, neutropenia, lymphocytosis, flatulence, constipation, pyrexia, lethargy, and irritability/agitation.

The most common adverse reactions reported with sodium phenylbutyrate tablets and powder (Buphenyl) not displayed above were amenorrhea/menstrual dysfunction (23%), body odor (3%), and taste aversion (3%). Similarly, the most common adverse reactions (≥ 3%) reported with sodium phenylbutyrate oral pellets (Pheburane) that are not listed above are amenorrhea or menstrual dysfunction, body odor, and dysgeusia.

SPECIAL POPULATIONS^{50,51,52,53}

Pediatrics

Carglumic acid (Carbaglu) has been evaluated in and is indicated for pediatric patients of all ages, from birth to adulthood.

Glycerol phenylbutyrate (Ravicti) is approved for use in pediatric patients of all ages.

Sodium phenylbutyrate tablets (Buphenyl) are approved for use in pediatric patients weighing > 20 kg. Sodium phenylbutyrate powder (Buphenyl) and pellets (Pheburane) may be used in younger patients.

Pregnancy

As there are no adequate and well-controlled studies or sufficient data regarding use of sodium phenylbutyrate (Buphenyl, Pheburane) in pregnant women to determine the drug-associated risk of adverse maternal or fetal outcomes, it should only be given if clearly needed. Untreated urea cycle disorders during pregnancy can lead to serious morbidity and mortality for the mother and fetus.

In compliance with the Pregnancy and Lactation Labeling Rule (PLLR), labeling for carglumic acid (Carbaglu) has been updated to remove the assigned Pregnancy Category (previously C) and replace this with descriptive text. Rare case reports of use of carglumic acid in pregnancy are insufficient to inform of a maternal or fetal drug-associated risk; however, untreated NAGS deficiency can result in irreversible damage, and potentially death, in pregnant women.

Glycerol phenylbutyrate (Ravicti) is not assigned a Pregnancy Category; data are insufficient to inform of a drug-associated risk or major birth defects and miscarriage.

Renal Impairment

Exposure to carglumic acid (Carbaglu) is increased in renal impairment. Detailed dosage adjustments for patients with moderate or severe renal impairment are provided in the labeling.

DOSAGES^{54,55,56,57}

Drug	Dosing	Available Strengths
carglumic acid (Carbaglu)	<p>Acute hyperammonemia (adults and pediatrics): 100 mg/kg/day to 250 mg/kg/day administered orally or by nasogastric (NG) tube divided into 2 to 4 doses and rounded to the nearest 100 mg; titrate based on plasma ammonia levels and symptoms</p> <p>Maintenance dose (adults and pediatrics): 10 mg/kg/day to 100 mg/kg/day administered orally or by nasogastric (NG) tube divided into 2 to 4 doses and rounded to the nearest 100 mg (half of a 200 mg tablet); titrate dose to target normal plasma ammonia level for age</p> <p>Acute hyperammonemia due to PA or MMA (adults and pediatrics):</p> <ul style="list-style-type: none"> ▪ Patients weighing ≤ 15 kg: 150 mg/kg/day ▪ Patients weighing > 15 kg: 3.3 g/m²/day <p>Divide into 2 equal doses, rounding up to the next multiple of 50 mg; administer doses at least 12 hours apart, continue treatment until ammonia level is < 50 micromol/L (for a maximum duration of 7 days)</p> <p>Disperse tablets in water only (≥ 2.5 mL/tablet) immediately before use; tablets should <i>not</i> be swallowed whole or crushed or mixed with any other foods or liquids</p> <p>When administering via an NG tube or oral syringe for pediatric patients, mix each tablet with 2.5 mL of water to yield a concentration of 80 mg/mL</p> <p>To ensure complete delivery, the mixing container (or oral syringe) should be rinsed with additional volumes of water and swallowed immediately; NG tubes should be flushed with additional water to clear the tube; oral syringes should be refilled with 1 to 2 mL of water and administered immediately to ensure complete administration</p> <p>NOTE: for mild renal impairment, no dosage adjustment is necessary; for moderate to severe renal impairment, refer to the package insert for dosing</p>	Tablet for oral suspension: 200 mg (scored)

Dosages (continued)

Drug	Dosing	Available Strengths
glycerol phenylbutyrate (Ravicti)	<p>Initial dose (phenylbutyrate-naïve): 4.5 to 11.2 mL/m²/day (5 to 12.4 g/m²/day) administered orally; those with residual enzyme activity not controlled with protein restriction should begin treatment at a dose of 4.5 mL/m²/day</p> <p>Based on protein intake, an initial estimate of 0.6 mL glycerol phenylbutyrate per gram of dietary protein/24 hours is needed</p> <p>Maintenance dose: Adjust dosage to produce a fasting plasma ammonia level less than half the upper limit of normal (ULN) based on age; if available, urinary phenylacetylglutamine (U-PAGN) and plasma phenylacetate also may be used to guide dosing, accounting for dietary protein intake and concomitant medications (see prescribing information for details)</p> <p>Conversion from sodium phenylbutyrate <i>powder</i> to glycerol phenylbutyrate:</p> <p style="padding-left: 20px;">Total daily dose = total daily dose of sodium phenylbutyrate (g) x 0.81</p> <p>Conversion from sodium phenylbutyrate <i>tablets</i> to glycerol phenylbutyrate:</p> <p style="padding-left: 20px;">Total daily dose = total daily dose of sodium phenylbutyrate (g) x 0.86</p> <p>Administer in 3 equally divided doses, each rounded to the nearest 0.5 mL (maximum dose, 17.5 mL/day) in patients ≥ 2 years or age; administer in 3 equally divided doses, each rounded to the nearest 0.1 mL (maximum dose, 17.5 mL/day) in patients < 2 years of age</p> <p>Administer with food (or formula or just prior to breastfeeding for infants) directly into the mouth or NG or gastrostomy (G-) tube via oral syringe or dosing cup; if administering via NG or gastrostomy (G)-tube, flush tube with 10 mL of water or formula and allow to drain, if needed, flush a second time with 10 mL of water after drug administration; for those requiring < 1 mL/dose via NG of G-tube, the delivered dose may be less than anticipated. Discard bottle and any unused product 28 days after opening.</p> <p>Must be used with dietary protein restriction and, in some cases, dietary supplements</p> <p>Patients with moderate to severe hepatic impairment should receive initial glycerol phenylbutyrate doses at the lower end of the initial dose range due to the potential for reduced metabolite conversion capability</p> <p>Follow patients clinically and with plasma ammonia levels for dose titration; closely monitor plasma ammonia levels during treatment and when changing the dosage (see prescribing information for details)</p>	Oral liquid: 1.1 g/mL (delivers 1.02 g/mL phenylbutyrate)

Dosages (continued)

Drug	Dosing	Available Strengths
sodium phenylbutyrate (Buphenyl)	<p>Maintenance dose: 450 to 600 mg/kg/day orally in patients weighing < 20 kg or 9.9 to 13 g/m²/day orally in larger patients; administer in 3 to 6 equally divided doses; safety and efficacy of doses > 20 g/day have not been established</p> <p>Use in combination with dietary protein restriction and, in some cases, essential amino acid supplementation</p> <p>The powder may be administered via the mouth, NG tube, or G-tube; mix powder with food (solid or liquid) for immediate use</p> <p>When dissolved in water, sodium phenylbutyrate powder has demonstrated stability for up to 1 week at room temperature or under refrigerated conditions</p>	<p>Tablet: 500 mg</p> <p>Powder: 3 g/dose (teaspoon); teaspoon and tablespoon measurement device included</p>
sodium phenylbutyrate (Pheburane)	<p>450 to 600 mg/kg/day orally in patients weighing < 20 kg or 9.9 to 13 g/m²/day orally in patients weighing ≥ 20 kg; administer in 3 to 6 equally divided doses taken with food; safety and efficacy of doses > 20 g/day have not been established</p> <p>Use in combination with dietary protein restriction and, in some cases, essential amino acid supplementation</p> <p>In patients with hepatic impairment, initiate therapy at the lower end of the recommended dosage range and maintain at the lowest dose needed to control plasma ammonia levels</p> <p>Measure the dose using only the calibrated spoon provided in the packaging; measures up to 3 grams of sodium phenylbutyrate in 0.25 gram increments</p> <p>Swallow the coated oral pellets with a drink (e.g., water, fruit juices, protein-free infant formulas) or sprinkle onto spoonful of apple sauce or carrot puree only; swallow immediately to minimize dissolution of coating</p> <p>Do not chew oral pellets or mix into liquids</p> <p>Discard any remaining portion 45 days after first opening of bottle</p>	<p>Oral pellets: 483 mg of sodium phenylbutyrate per 1 gram of oral pellets (84 grams per bottle)</p>

Plasma levels of ammonia, arginine, branched-chain amino acids, and serum proteins should be maintained within normal limits, and plasma glutamine should be maintained at levels < 1,000 µmol/L. Monitor drug levels of phenylbutyrate and its metabolites, phenylacetate and phenylacetylglutamine, periodically.

CLINICAL TRIALS

Search Strategy

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, comparative, controlled trials comparing agents within this class for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. Due to paucity of data, open-label data crucial to product approval have been included. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-

up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

carglumic acid (Carbaglu)

Carglumic acid earned its indication for use in those with hyperammonemia due to PA and MMA through a double-blind, placebo-controlled, multicenter clinical trial.⁵⁸ The trial enrolled 90 patients with hyperammonemia (defined as a plasma ammonia level ≥ 70 micromol/L) who were admitted to a hospital. All patients received standard of care, (e.g., combination of protein restriction, intravenous glucose, insulin, and/or L-carnitine). Patients were randomized 1:1 to approved doses of carglumic acid or placebo for up to 7 days. The primary endpoint of median time to plasma ammonia level ≤ 50 micromol/L (normal range) or hospital discharge, whichever occurred first, was reached in 1.5 days in the carglumic acid group versus 2 days in the placebo group (95% confidence interval [CI], -1.2 to 0.1). The endpoint was most impacted by normalization of plasma ammonia levels.

A retrospective, unblinded, uncontrolled review of 23 patients was utilized to establish the safety and efficacy of carglumic acid for the treatment of hyperammonemia due to NAGS deficiency.⁵⁹ Prospective, controlled trials with carglumic acid have not been published.

glycerol phenylbutyrate (Ravicti) versus sodium phenylbutyrate (Buphenyl) in adults

A randomized, double-blind, crossover, noninferiority study compared glycerol phenylbutyrate to sodium phenylbutyrate in adults with confirmed deficiencies in CPS, OTC, or AS who had been on maintenance sodium phenylbutyrate prior to study enrollment (n=45).^{60,61} Eligible patients were required to have normal ammonia levels prior to enrollment, and drugs with the potential to increase ammonia (e.g., valproate), affect renal clearance (e.g., probenecid), or increase protein catabolism (e.g., corticosteroids) were not allowed. Patients were randomized 1:1 to either sodium phenylbutyrate for 2 weeks or glycerol phenylbutyrate for 2 weeks, each administered 3 times daily with meals and dosed to provide identical amounts of the PBA metabolite. Patients were required to adhere to a low-protein diet and received amino acid supplements. Following the first 2 weeks of therapy, participants were switched to the opposite treatment arm. The mean age of those enrolled was 33 years (range, 18 to 75 years), 69% were female, 33% had adult-onset disease, 89% had OTC deficiency, 7% had ASS deficiency, and 4% had CPS deficiency. The primary endpoint was the 24-hour area under the concentration curve (AUC₂₄; ammonia exposure in 24 hours) on days 14 and 28. Glycerol phenylbutyrate would be defined as noninferior if the upper limit of the 2-sided 95% confidence interval (CI) for the ratio of the geometric means (glycerol phenylbutyrate/sodium phenylbutyrate) was ≤ 1.25 . The mean AUC₂₄ for venous ammonia were 866 $\mu\text{mol}\cdot\text{h}/\text{L}$ and 977 $\mu\text{mol}\cdot\text{h}/\text{L}$ for glycerol phenylbutyrate and sodium phenylbutyrate, respectively (ratio, 0.91; 95% CI, 0.8 to 1.04). Thus, glycerol phenylbutyrate met the prespecified noninferiority margin. Ammonia values were standardized across various laboratories.

glycerol phenylbutyrate (Ravicti) in adults – long-term data

A 12 month, open-label, uncontrolled extension study evaluated the role of glycerol phenylbutyrate in 51 adults with UCDs by monthly measurement of venous ammonia levels.^{62,63} During the 12 months,

mean levels were within normal limits (range, 6 to 30 $\mu\text{mol/L}$). During the treatment period, 10 hyperammonemic crises occurred in 7 patients (14%).

Another open-label, single-arm, long-term trial (mean duration, 1.9 years; range, 0 to 4.5 years) assessed ammonia control with glycerol phenylbutyrate in 43 patients.⁶⁴ Mean fasting levels of ammonia, assessed at ≤ 6 month intervals, were within normal limits. Nine patients (21%) reported a total of 21 incidents of hyperammonemic crises.

glycerol phenylbutyrate (Ravicti) versus sodium phenylbutyrate (Buphenyl) in pediatric patients

Two, fixed-sequence, open-label, crossover trials compared the efficacy of glycerol phenylbutyrate to sodium phenylbutyrate in pediatric patients ages 2 to 17 years old ($n=22$; 4 patients under the age of 2 years were excluded due to lack of data).^{65,66,67,68} Study 1 ($n=11$) was a 7 day trial in patients 6 to 17 years old. Study 2 ($n=11$) was a 10 day trial in patients 2 to 5 years old. During the trial, patients were required to adhere to low-protein diets and were administered either glycerol phenylbutyrate or sodium phenylbutyrate at doses designed to provide equivalent PBA exposure (mean glycerol phenylbutyrate dose 7.9 mL/day; range, 1.4 to 17.4). Enrolled patients included 12 with OTC, 8 with ASL, and 2 with ASS. AUC_{24} was found to be similar in both groups. In Study 1, the mean AUC_{24} was 604 $\mu\text{mol-h/L}$ and 815 $\mu\text{mol-h/L}$ in patients treated with glycerol phenylbutyrate and sodium phenylbutyrate, respectively. In Study 2, the mean AUC_{24} was 632 $\mu\text{mol-h/L}$ and 720 $\mu\text{mol-h/L}$ in patients treated with glycerol phenylbutyrate and sodium phenylbutyrate, respectively. Ammonia values were standardized across various laboratories.

An integrated analysis included pediatric data in patients 2 months to < 2 years of age in 1 of the above studies and another open-label, single-arm study ($n=17$).⁶⁹ Enrolled patients were 2 months to 2 years of age and had diagnosed or clinically suspected UCD (all subtypes, excluding NAGS). Patients were switched to ($n=15$) or started ($n=2$) glycerol phenylbutyrate; dosage was based on prior treatment status and whether or not the patient was presenting in hyperammonemic crisis with a mean duration of 8.85 months (range, 6 days to 18.4 months). Efficacy was determined using retrospective data up to 12 months prior to the switch and prospective data. Hyperammonemic crises occurred 36 times in 11 patients before glycerol phenylbutyrate therapy and 11 times in 7 patients while on glycerol phenylbutyrate (reduction from 2.98 to 0.88 episodes per year). An extension study of limited numbers suggests ongoing efficacy.

glycerol phenylbutyrate (Ravicti) in pediatric patients – long-term data

Two, 12 month, open-label, uncontrolled extension studies evaluated the long-term efficacy of glycerol phenylbutyrate ($n=26$) in pediatric patients ages 6 to 17 years.^{70,71} During the 12 months, mean levels were within normal limits (range, 17 to 23 $\mu\text{mol/L}$). During the treatment period, 5 hyperammonemic crises occurred in 5 patients (19%).

An open-label, single-arm study in patients ages 1 to 17 years with UCD assessed the long-term efficacy of glycerol phenylbutyrate ($n=45$; median duration, 1.7 years [range, 0.2 to 4.6 years]).⁷² Mean fasting levels of ammonia, assessed at ≤ 6 month intervals, were within normal limits. Eleven patients (24%) reported a total of 22 incidents of hyperammonemic crises.

The safety and efficacy of glycerol phenylbutyrate was assessed in a total of 16 patients < 2 months old (median, 0.5 months; range, 0.1 to 2 months).⁷³ Ten of the 16 patients were transitioned from sodium

phenylbutyrate, 3 were treatment-naïve, and 3 transitioned from intravenously administered sodium benzoate and sodium phenylacetate. Glycerol phenylbutyrate treatment was adjusted to normalize ammonia levels. During the safety phase (months 1 through 24), ammonia levels were monitored monthly for the first 6 months and every 3 months thereafter. During this phase, ammonia levels varied from a median of 36 to 72 $\mu\text{mol/L}$ at monthly measures (normal range, 28 to 57 $\mu\text{mol/L}$), 1 patient withdrew due to increased hepatic enzymes, and 5 patients (all < 1 month old) reported a total of 7 incidents of hyperammonemic crises.

sodium phenylbutyrate (Buphenyl) in pediatric patients

The efficacy of sodium phenylbutyrate was studied of 32 females < 18 years of age with OTC deficiency with at least 1 episode of encephalopathy who were referred to Johns Hopkins Hospital.⁷⁴ Patients were ultimately treated in collaboration by a more local institution. Patients were assigned to treatment consisting of sodium benzoate alone (n=11) or in combination with sodium phenylacetate or sodium phenylbutyrate (n=22) or sodium phenylbutyrate alone (n=28). Five-year survival was $\geq 90\%$, and the frequency of hyperammonemic episodes decreased as age increased as well as in the group treated with sodium phenylacetate or sodium phenylbutyrate. Cognitive testing remained stable in 19 of 23 patients with available data.

SUMMARY

Urea cycle disorders (UCDs) are inherited deficiencies of enzymes or transporters that function in the synthesis of urea from ammonia within the body. UCDs are most often related to the first 4 enzymes within the cycle: carbamyl phosphate synthetase (CPS), ornithine transcarbamylase (OTC), argininosuccinate synthetase (AS), and argininosuccinate lyase (ASL). They may also result from a deficiency in N-acetylglutamate synthetase (NAGS), the enzyme for the cofactor in N-acetylglutamate production. Arginase deficiency also affects urea production as arginase is required in the last step of urea production. The inability to synthesize urea due to a UCD leads to accumulation of ammonia in the blood, or hyperammonemia, which can be fatal if not recognized and managed immediately. Prior to the FDA approval of agents in this class, most patients were treated symptomatically. In addition, protein restriction is fundamental to treatment of these disorders.

Carglumic acid (Carbaglu) is a synthetic structural analogue of endogenous N-acetylglutamate (NAG) approved for patients with NAGS deficiency both for the acute and maintenance treatment of hyperammonemia and as an adjunctive therapy to the standard of care for those patients with acute hyperammonemia due to propionic acidemia (PA) or methylmalonic acidemia (MMA). It is available as an oral tablet and is administered in divided doses 2 to 4 times per day. It may be administered orally or by a nasogastric tube.

Glycerol phenylbutyrate (Ravicti) and sodium phenylbutyrate (Buphenyl, **Pheburane**) provide an alternate pathway for excretion of nitrogen, functioning as nitrogen scavengers. Both are approved for the chronic management of patients with UCDs, but sodium phenylbutyrate is approved specifically for those with deficiencies of CPS, OTC, or AS. Glycerol phenylbutyrate is available as an oral liquid and is administered in 3 equally divided doses. Sodium phenylbutyrate is available as either a tablet or powder for dissolution, as brand Buphenyl, **and as oral pellets, as brand Pheburane**; both are administered in 3 to 6 equally divided doses. Tablets **and pellets** are intended for oral use in those able to swallow but the liquid may be administered orally, via nasogastric tube, or via a gastrostomy tube.

Glycerol phenylbutyrate is approved in patients of all ages; however, due to the rarity of the disorder, data are limited in any one population and particularly in older adults. The major metabolite of glycerol phenylbutyrate and sodium phenylbutyrate, PAA, may cause neurotoxicity.

The most common adverse effects associated with these agents include gastrointestinal adverse effects and headache. Infections have also been reported with carglumic acid. Rash has been reported with all agents.

High-quality published comparative literature is limited. All have demonstrated efficacy as measured by ammonia levels in clinical trials. Glycerol phenylbutyrate was evaluated in patients stabilized on sodium phenylbutyrate and demonstrated similar serum ammonia control. Likewise, suggested management guidelines do not suggest the use of any one agent over another; however, some products are approved by enzyme deficiency and corresponding published data within that population.

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