BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

CARBAGLU® (carglumic acid) oral
Carglumic acid oral
Glycerol Phenylbutyrate oral
OLPRUVA™ (sodium phenylbutyrate) oral
RAVICTI® (glycerol phenylbutyrate) oral
Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and/or Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Medical Necessity Requirements for CARBAGLU (carglumic acid) and Carglumic Acid generic

Criteria for Initial Therapy:

Prescriber Qualifications
- Prescribed by a physician specializing in metabolic disorders or is in consultation with one

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Indication

- **ONE** of the following:
  - Acute hyperammonemia due to **propionic acidemia (PA)** or **methylmalonic acidemia (MMA)** used as adjunctive therapy to standard of care
  - Acute hyperammonemia due to **N acetylglutamate synthase (NAGS) deficiency** used as adjunctive therapy to standard of care
  - Chronic hyperammonemia due to **N acetylglutamate synthase (NAGS) deficiency** used as maintenance therapy

Age Requirement

- Newborn or older

Brand Specific Criteria

- **For Carbaglu (carglumic acid):** Failure (trial for at least three months duration), contraindication per FDA label, intolerance, or is not a candidate for **generic carglumic acid. Note**: Failure, contraindication, or intolerance to the generic should be reported to the FDA (see Definitions section)

Additional Requirements

- Does not have end stage renal disease (creatinine clearance less than 15 mL per minute/1.73 meters^2)

Documentation Requirements

- A completed request form must be submitted including:
  - Chart notes
  - Lab results
  - Supporting clinical documentation

Initial Therapy Criteria Approval Duration

- **For Acute Hyperammonemia due to PA or MMA:** Until ammonia level is less than 50 micromol/L AND for a maximum duration of 7 days OR end of plan year
- **For Hyperammonemia due to NAGS deficiency:** 12 months OR end of plan year

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Criteria for Continuation of Therapy (renewal therapy):

Note: Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy.

Prescriber Qualifications

- Continues to be seen by a physician specializing in metabolic disorders or is in consultation with one

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Clinical Response
- Plasma ammonia levels are within the normal range for age and clinical condition

Adherence
- Adherence to medication and dietary protein restriction has been documented

Brand Specific Criteria
- **For Carbaglu (carglumic acid):** Failure (trial for at least three months duration), contraindication per FDA label, intolerance, or is not a candidate for **generic carglumic acid. Note**: Failure, contraindication, or intolerance to the generic should be reported to the FDA (see Definitions section)

Additional Requirements
- Does not have end stage renal disease (creatinine clearance less than 15 mL per minute/1.73 meters^2)

Documentation Requirements
- Chart notes
- Lab results (plasma ammonia levels)
- Supporting clinical documentation

Continuation Therapy Criteria Approval Duration
- 12 months OR end of plan year

Medical Necessity Requirements for: Glycerol Phenylbutyrate generic, OLPRUVA (sodium phenylbutyrate), and RAVICTI (glycerol phenylbutyrate)

Criteria for Initial Therapy:

Prescriber Qualifications
- Prescribed by a physician specializing in metabolic disorders or is in consultation with one

Indication
- Urea cycle disorder with chronic hyperammonemia, confirmed by enzymatic, biochemical, or genetic testing due to **ONE** of the following enzyme deficiencies:
  - Carbamylphosphate synthetase (CPS)
  - Ornithine transcarbamylase (OTC)
  - Argininosuccinic acid synthetase (AS)

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Age Requirement

- Newborn or older
- **Additionally for Olpruva only:** weight of 20 kg or greater AND body surface area of 1.2 m² or greater

Brand Specific Criteria

- **For ALL agents:** Failure (trial for at least three months duration), contraindication per FDA label, intolerance, or is not a candidate for **generic sodium phenylbutyrate. Note**: Failure, contraindication, or intolerance to the generic should be reported to the FDA (see Definitions section)
- **Additionally for Ravicti** (glycerol phenylbutyrate): Failure (trial for at least three months duration), contraindication per FDA label, intolerance or is not a candidate for **generic glycerol phenylbutyrate**. **Note**: Failure, contraindication, or intolerance to the generic should be reported to the FDA (see Definitions section)
- **Additionally for Olpruva** (sodium phenylbutyrate): Failure, contraindication per FDA label, intolerance, or is not a candidate for **THREE** generic equivalents (if available) each used for at least three months. **Note**: Failure, contraindication, or intolerance to the generic should be reported to the FDA (see Definitions section)

Safety

- There is **NONE** of the following:
  - No known hypersensitivity to phenylbutyrate
  - Combination use of glycerol phenylbutyrate, Ravicti, Olpruva, or sodium phenylbutyrate
  - Neurotoxicity
  - New onset or worsening edema (Olpruva only)

Additional Requirements

- Must be used with a protein restricted diet and, in some cases, dietary supplements (essential amino acids, arginine, citrulline, protein free calorie supplements)
- No use in treatment of **EITHER** of the following:
  - Acute hyperammonemia
  - N acetylglutamate synthase (NAGS) deficiency

Documentation Requirements

- A completed request form must be submitted including:
  - Chart notes
  - Lab results (plasma ammonia levels)
  - Supporting clinical documentation

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Initial Therapy Criteria Approval Duration
- 12 months OR end of plan year

Criteria for Continuation of Therapy (renewal therapy):

Note: Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy.

Prescriber Qualifications
- Continues to be seen by a physician specializing in metabolic disorders or is in consultation with one

Clinical Response
- Plasma ammonia levels are within normal range for age using assay specific and therapeutic target ranges

Brand Specific Criteria
- **For Ravicti** (glycerol phenylbutyrate): Failure (trial for at least three months duration), contraindication per FDA label, intolerance or is not a candidate for **generic glycerol phenylbutyrate**. **Note**: Failure, contraindication, or intolerance to the generic should be reported to the FDA (see Definitions section)
- **For Olpruva** (sodium phenylbutyrate): Failure, contraindication per FDA label, intolerance, or is not a candidate for **THREE** generic equivalents (if available) each used for at least three months. **Note**: Failure, contraindication, or intolerance to the generic should be reported to the FDA (see Definitions section)

Adherence
- Adherence to medication, protein restricted diet, and/or dietary supplements has been documented

Safety
- There is **NONE** of the following:
  - No known hypersensitivity to phenylbutyrate
  - Combination use of glycerol phenylbutyrate, Ravicti, Olpruva, or sodium phenylbutyrate
  - Neurotoxicity
  - New onset or worsening edema (Olpruva only)

Additional Requirements
- Must be used with a protein restricted diet and, in some cases, dietary supplements (essential amino acids, arginine, citrulline, protein free calorie supplements)
- No use in treatment of **EITHER** of the following:
  - Acute hyperammonemia
  - N acetylglutamate synthase (NAGS) deficiency

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Documentation Requirements

- Chart notes
- Lab results (plasma ammonia levels)
- Supporting clinical documentation

Continuation Therapy Criteria Approval Duration

- 12 months OR end of plan year

Criteria for Off-Label Use Requests:

Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. Off-Label Use of Non-Cancer Medications

2. Off-Label Use of Cancer Medications

Description:

Carglumic acid (brand Carbaglu and generic) is indicated as an adjunctive therapy in pediatric and adult patients for the treatment of acute hyperammonemia due to the deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS) and is indicated for maintenance therapy in pediatric and adult patients for chronic hyperammonemia due to the deficiency of the hepatic enzyme NAGS. It is a synthetic structural analog of N-acetylglutamate (NAG), a co-factor necessary for functioning of the urea cycle that is absent in patients with NAGS deficiency. Carglumic acid acts as a replacement for NAG in NAGS deficiency by activating carbamoyl phosphate synthetase 1 (CPS 1). There are only 50 known cases of NAGS deficiency worldwide.

Olpruva (sodium phenylbutyrate) is a nitrogen-binding agent indicated as 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 (BSA) of 1.2 m2 or greater, with urea cycle disorders (UCDs) involving deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid synthetase (AS). Olpruva (sodium phenylbutyrate) is not indicated for the treatment of acute hyperammonemia.

Glycerol phenylbutyrate (brand Ravicti and generic) is indicated for use as a nitrogen binding agent for the chronic management of adult and pediatric individuals 2 months of age and older with urea cycle disorder (UCD) who cannot be managed by dietary protein restriction and/or amino acid supplements alone. Glycerol phenylbutyrate must be used with dietary protein restriction and in some cases dietary supplements (such as essential amino acids, arginine, citrulline, protein-free calorie supplements). Glycerol phenylbutyrate is not indicated for the

treatment of acute hyperammonemia in patients with UCDs. The safety and efficacy of glycerol phenylbutyrate for the treatment of NAGS deficiency has not been established.

Glycerol phenylbutyrate is a triglyceride containing 3 molecules of phenylbutyrate (PBA) to phenylacetic acid (PAA). PAA binds with glutamine in the liver and kidneys to form phenylacetylglutamine (PAGN) and provides an alternative pathway for elimination of nitrogen, which is excreted by the kidneys. If available, the ratio of plasma PAA to PAGN may help guide glycerol phenylbutyrate dosing. In general, a high PAA to PAGN ratio may indicate a slower or less efficient conjugation reaction to form PAGN, which may lead to increased PAA levels and neurologic symptoms. The PAA to PAGN ration has generally been less than 1 in UCDs who do not have significant plasma PAA accumulation. Glycerol phenylbutyrate is available as an oral liquid preparation.

Sodium phenylbutyrate is also a pro-drug and is rapidly metabolized to the PAA that binds with glutamine to form PAGN. Sodium phenylbutyrate is available as brand Buphenyl and also as a generic tablet and powder formulations. It is FDA approved as adjunctive therapy in the chronic management of patients with UCD involving deficiencies of carbamyl phosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid synthetase (AS). 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.

Urea Cycle Disorders (UCD) is a genetic disorder caused by a mutation(s) that result in a deficiency of one or more the enzymes or transporters involved in the urea cycle. The urea cycle is responsible for elimination of nitrogen that is formed from the breakdown of proteins and other nitrogen containing compounds. In UCD, nitrogen accumulates in the form of ammonia resulting in hyperammonemia. UCD is characterized by the accumulation of nitrogen and results in life-threatening ammonia levels and neurologic injury. Hyperammonemia is the major cause of morbidity and mortality in UCD patients, and outcome during hyperammonemic crises is related to blood ammonia levels. The incidence of UCD is estimated to be approximately 1:8200 live births.

The mainstays of treatment are: 1) reduce plasma ammonia concentration; 2) pharmacologic management to allow alternative pathway excretion of excess nitrogen; 3) reduce the amount of excess nitrogen in the diet; 4) reduce catabolism through the introduction of calories supplied by carbohydrates and fat; and 5) reduce the risk of neurologic damage.

The treatment of NAGS deficiency is aimed at preventing excessive ammonia from being formed or removing excessive ammonia during a hyperammonemic episode. Long-term therapy for NAGS deficiency combines dietary restrictions and the stimulation of alternative methods of converting and excreting nitrogen from the body (alternative pathways therapy). NAG is the product of NAGS, a mitochondrial enzyme. NAG is an essential allosteric activator of carbamoyl phosphate synthetase 1 (CPS 1) in liver mitochondria. CPS 1 is the first enzyme of the urea cycle.

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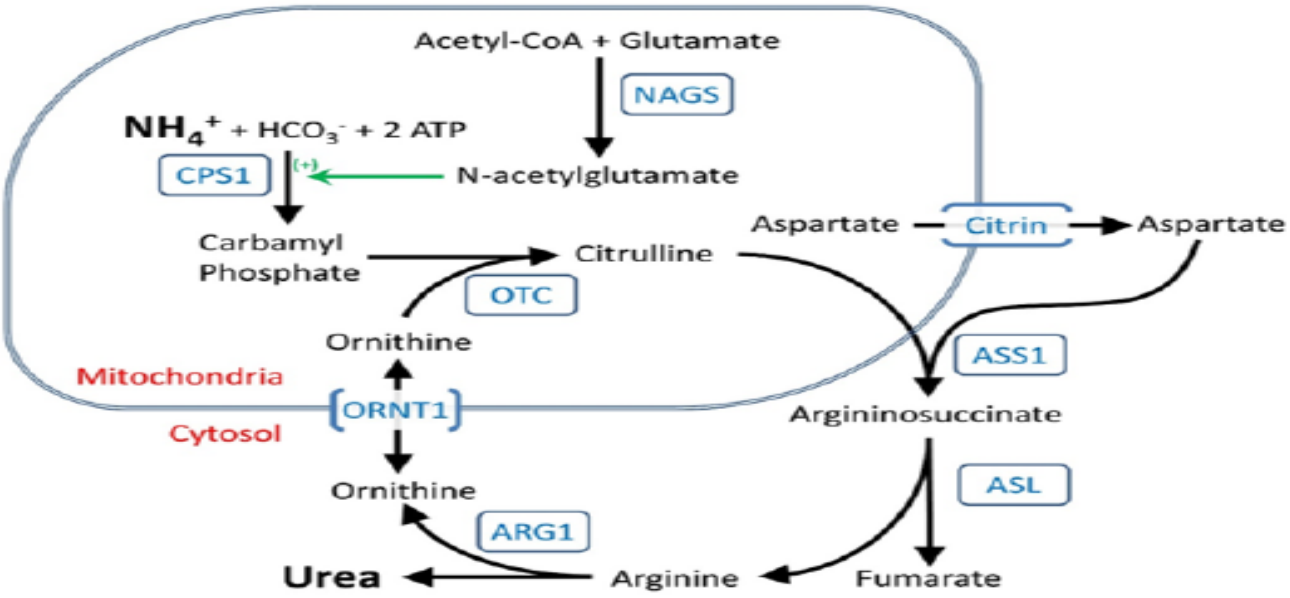
Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

Enzyme deficiencies associated with urea cycle disorder:

CPS1 - Carbamyl phosphate synthetase deficiency
NAGS - N-acetylglutamate synthetase deficiency
OTC - Ornithine transcarbamylase deficiency
AAS or ASS - Argininosuccinic acid synthetase deficiency (Citrullinemia)
AL or ASL or ASA Lyase - Argininosuccinate lyase deficiency (Argininosuccinic Aciduria)
AG or ARG1 or ARGD – Arginase deficiency
ORNT1 - Ornathine translocase or ornithine transporter mitochondrial 1 deficiency
CITRIN - Aspartate glutamate translocation deficiency



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Resources:

Carbaglu (carglumic acid) tablet for suspension product information, revised by Recordati Rare Diseases 01-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed October 30, 2025.

Carglumic acid tablet for suspension product information, revised by Burel Pharmaceuticals, LLC. 03-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed October 30, 2025.

Olpruva (sodium phenylbutyrate) pellets for oral suspension product information, revised by Acer Therapeutics, Inc. 12-2022. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed October 30, 2025.

Ravicti (glycerol phenylbutyrate) liquid product information, revised by Horizon Therapeutics, Inc. 09-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed October 30, 2025.

Glycerol phenylbutyrate liquid product information, revised by Par Health USA, LLC. 04-2025. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed January 04, 2026.

Lee B. Urea cycle disorders: Management. In: UpToDate, Kritzer A, Kremen J (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through December 2025. Topic last updated November 11, 2025. Accessed January 04, 2026.

Lee B. Urea cycle disorders: Clinical features and diagnosis. In: UpToDate, Kaplan S, Kremen J (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through December 2025. Topic last updated October 13, 2023. Accessed January 04, 2026.

Häberle J, Burlina A, Chakrapani A, et al. Suggested guidelines for the diagnosis and management of urea cycle disorders: First revision. J Inherit Metab Dis. 2019;42: 1192–1230. https://doi.org/10.1002/jimd.12100. Accessed January 12, 2023. Re-evaluated January 4, 2026.