BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

CARBAGLU® (carglumic acid) oral
Carglumic acid 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 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.

Criteria:

CARBAGLU® (carglumic acid)
Carglumic acid oral

- **Criteria for initial therapy**: Carbaglu (carglumic acid) and generic carglumic acid are considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a physician experienced in metabolic disorders

2. Individual has a confirmed diagnosis of hyperammonemia due to **ONE** of the following:
    a. Adjunctive therapy to standard of care for the treatment of **acute** hyperammonemia due to deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS)
    b. Adjunctive therapy to standard of care for the treatment of **acute** hyperammonemia due to propionic acidemia (PA) or methylmalonic acidemia (MMA)
    c. Maintenance therapy for the treatment of **chronic** hyperammonemia due to NAGS deficiency

3. **For Carbaglu (carglumic acid):** Individual has failure after adequate trial, 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)

Initial approval duration:
For Hyperammonemia due to NAGS deficiency:
12 months
For Acute Hyperammonemia due to PA or MMA:
Until the ammonia level is less than 50 micromol/L **and** for a maximum duration of 7 days

- **Criteria for continuation of coverage (renewal request):** Carbaglu (carglumic acid) and generic carglumic acid are considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a physician experienced in metabolic disorders

2. Individual's condition has responded while on therapy with response defined as plasma ammonia levels are within the normal range for the patient's age and their clinical condition

3. **For Carbaglu (carglumic acid):** Individual has failure after adequate trial, 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)

4. Individual has been adherent with the medication and dietary protein restriction

Renewal duration:
For Hyperammonemia due to NAGS deficiency:
12 months

- 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**

OLPRUVA™ (sodium phenylbutyrate)
RAVICTI® (glycerol phenylbutyrate)

- **Criteria for initial therapy**: Ravicti (glycerol phenylbutyrate), Olpruva (sodium phenylbutyrate), and/or generic equivalent (if available) are considered ***medically necessary*** when **ALL** of the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a physician experienced in metabolic disorders

2. Individual has a confirmed diagnosis of urea cycle disorder with chronic hyperammonemia due to at least **ONE** urea cycle enzyme deficiencies involving carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC) or argininosuccinic acid synthetase (AS) confirmed by enzymatic, biochemical, or genetic testing

3. **Additional criteria for Olpruva (sodium phenylbutyrate) only**: Individual weighs 20 kg or greater and has a body surface area 1.2 m^2 or greater

4. Must be used with a protein restricted diet and in some cases, dietary supplements (such as essential amino acids, arginine, citrulline, protein-free calorie supplements)

5. Individual has failure, contraindication per FDA label, intolerance, or is not a candidate for generic sodium phenylbutyrate

6. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

7. Individual does **not** have acute hyperammonemia

8. Individual does **not** have N-acetylglutamate synthase (NAGS) deficiency

9. Individual does not have the FDA-label contraindication of known hypersensitivity to phenylbutyrate

10. Ravicti (glycerol phenylbutyrate), Olpruva (sodium phenylbutyrate), or other sodium phenylbutyrate products will not be used in combination

Initial approval duration: 12 months

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- **Criteria for continuation of coverage (renewal request):** Ravicti (glycerol phenylbutyrate), Olpruva (sodium phenylbutyrate), and/or generic equivalent (if available) are considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met **(samples are not considered for continuation of therapy)**:

  1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a physician experienced in metabolic disorders

  2. Individual's condition has responded while on therapy with response defined as plasma ammonia levels are within the normal range for the patient's age using the assay-specific normal ranges and the therapeutic target ranges for plasma ammonia

  3. Individual has failure, contraindication per FDA label, intolerance, or is not a candidate for generic sodium phenylbutyrate

  4. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

  5. Individual has been adherent with the medication, protein restriction diet and/or dietary supplements (such as essential amino acids, arginine, citrulline, protein-free calorie supplements)

  6. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use as follows:
     a. Contraindications as listed in the criteria for initial therapy section
     b. Adverse drug effects such as neurotoxicity
     c. New-onset edema or worsening edema while on Olpruva (sodium phenylbutyrate)

  7. Ravicti (glycerol phenylbutyrate), Olpruva (sodium phenylbutyrate), or other sodium phenylbutyrate products will not be used in combination

  Renewal duration: 12 months

- 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**

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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.

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

Ravicti (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 Ravicti (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. Ravicti (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.

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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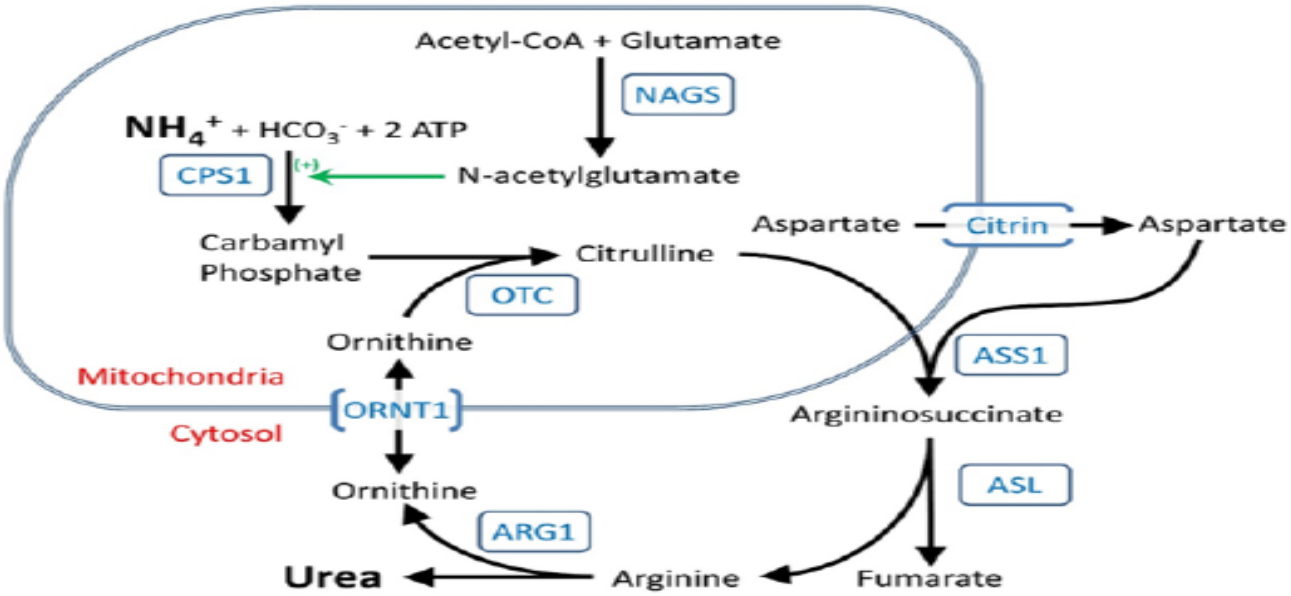

Resources:

Carbaglu (carglumic acid) tablet for suspension product information, revised by Recordati Rare Diseases 01-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed November 11, 2024.

Carglumic acid tablet for suspension product information, revised by Burel Pharmaceuticals, LLC. 03-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed November 11, 2024.

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 November 11, 2024.

Ravicti (glycerol phenylbutyrate) liquid product information, revised by Horizon Therapeutics, Inc. 09-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed November 11, 2024.

Lee B. Urea cycle disorders: Management. In: UpToDate, Hahn S, TePas E (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through November 2024. Topic last updated November 18, 20. Accessed December 27, 2024.

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 December 27, 2024.