



An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINES  
SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 7/16/2015  
LAST REVIEW DATE: 2/17/2022  
LAST CRITERIA REVISION DATE: 2/17/2022  
ARCHIVE DATE:

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## CARBAGLU® (carglumic acid) oral Carglumic Acid oral RAVICTI® (glycerol phenylbutyrate) oral

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Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

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This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at [www.azblue.com/pharmacy](http://www.azblue.com/pharmacy).

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the [request form](#) in its entirety with the chart notes as documentation. **All requested data must be provided.** Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602)



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864-3126 or emailed to [Pharmacyprecert@azblue.com](mailto:Pharmacyprecert@azblue.com). Incomplete forms or forms without the chart notes will be returned.

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### Criteria:

## CARBAGLU (carglumic acid) Carglumic Acid

➤ **Criteria for initial therapy:** Carglumic acid (brand Carbaglu and generic) is 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. A confirmed diagnosis of urea cycle disorder with 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. Maintenance therapy for the treatment of chronic hyperammonemia due to NAGS deficiency
  - c. Adjunctive therapy to standard of care for the treatment of acute hyperammonemia due to propionic acidemia (PA) or methylmalonic acidemia (MMA)
3. Individual has failure, contraindication per FDA label, or intolerance to the following:
  - a. **For acute hyperammonemia:** sodium benzoate/sodium phenylacetate injection
  - b. **For chronic hyperammonemia:** generic sodium phenylbutyrate
4. Individual does not have end stage renal disease

### 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):** Carglumic acid (brand Carbaglu and generic) is considered *medically necessary* and will be approved when **ALL** of the following criteria are met:



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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 responded while on therapy
  - a. Response is defined as:
    - i. For Hyperammonemia due to NAGS deficiency:
      1. Plasma ammonia levels are within the normal range for the patient's age and their clinical condition
3. Individual has been adherent with the medication and dietary protein restriction
4. Individual does not have end stage renal disease

**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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## RAVICTI (glycerol phenylbutyrate)

➤ **Criteria for initial therapy:** Ravicti (glycerol phenylbutyrate) is 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. A confirmed diagnosis of chronic urea cycle disorder with hyperammonemia due to at least **ONE** urea cycle enzyme deficiency confirmed by enzymatic, biochemical, or genetic testing
3. Individual does not have acute hyperammonemia
4. Individual does not have N-acetylglutamate synthase (NAGS) deficiency
5. Dietary protein restriction and/or amino acid supplementation alone have not been effective



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6. 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)
7. Individual has failure, contraindication per FDA label, or intolerance to generic sodium phenylbutyrate
8. There are **NO** FDA-label contraindications, such as:
  - a. Known hypersensitivity to phenylbutyrate
9. Individual does not have impaired renal function

**Initial approval duration:** 12 months

➤ **Criteria for continuation of coverage (renewal request):** Ravicti (glycerol phenylbutyrate) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

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 responded while on therapy
  - a. Response is defined as:
    - i. 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 been adherent with the medication, protein restriction diet and/or dietary supplements (such as essential amino acids, arginine, citrulline, protein-free calorie supplements)
4. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use
  - a. Contraindications as listed in the criteria for initial therapy section
  - b. Significant adverse effect such as:
    - i. Neurotoxicity: signs and symptoms may include nausea, vomiting, headache, fatigue, lightheadedness, dysgeusia, hypoacusis, somnolence, disorientation, confusion, impaired memory, and exacerbation of preexisting neuropathy, tremor, dizziness, seizure in the absence of high plasma ammonia levels or intercurrent illness to explain these symptoms
5. Individual does not have impaired renal function
6. There are no significant interacting drugs

**Renewal duration:** 12 months



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### **Carglumic Acid oral**

## **RAVICTI® (glycerol phenylbutyrate) oral**

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➤ 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.

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.



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## **CARBAGLU® (carglumic acid) oral**

### **Carglumic Acid oral**

## **RAVICTI® (glycerol phenylbutyrate) oral**

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### **Urea Cycle Disorders (UCD):**

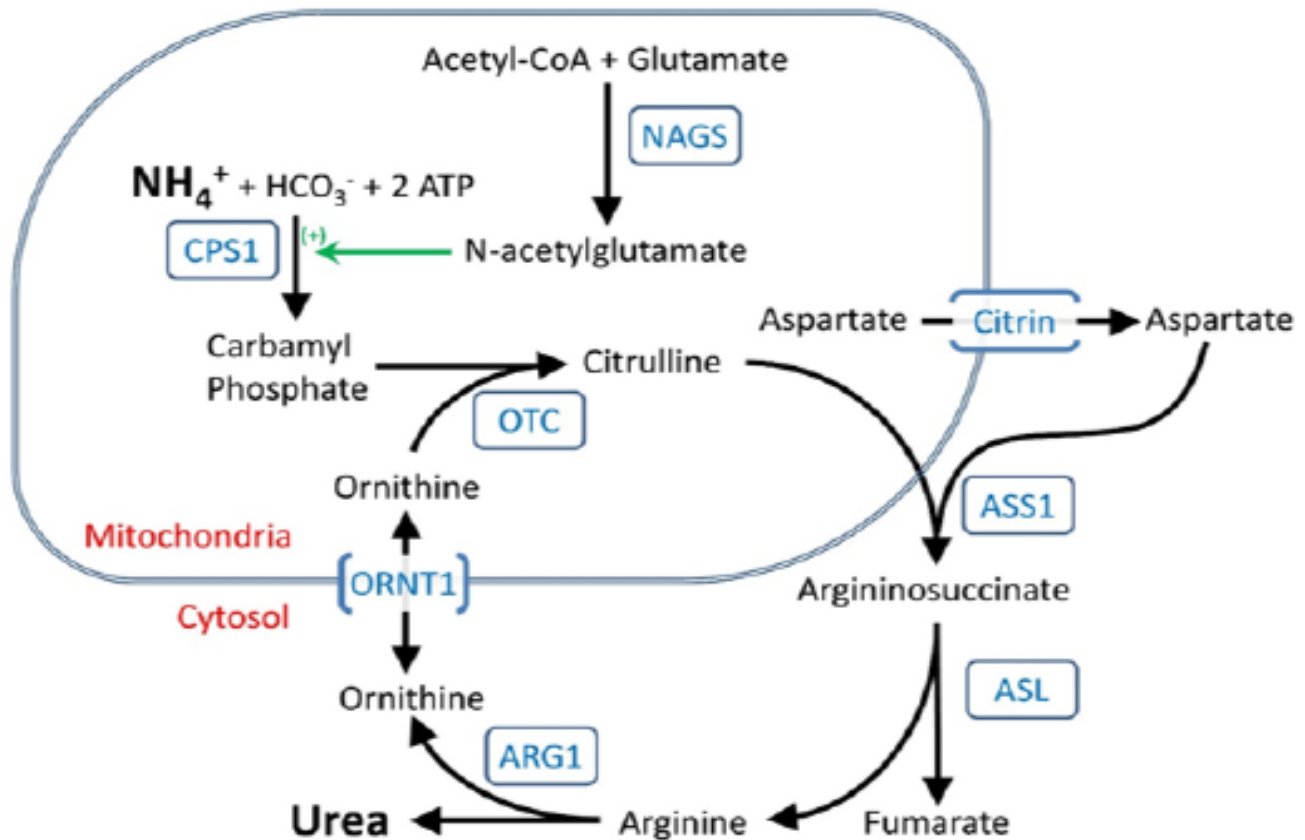
- UCD is a genetic disorder caused by a mutation(s) that result in a deficiency of one or more the enzymes or transporters involved in the urea cycle
- The urea cycle is responsible for elimination of nitrogen that is formed by the breakdown of proteins and other nitrogen containing compounds
- In UCD, nitrogen accumulates in the form of ammonia, a highly toxic substance, resulting in hyperammonemia
- UCD is characterized by 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
  - 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:**

**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 - Ornithine 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 08-2021. Available at DailyMed <http://dailymed.nlm.nih.gov>. Accessed December 30, 2021.

Carglumic acid tablet for suspension product information, revised by Eton Pharmaceuticals, Inc. 12-2021. Available at DailyMed <http://dailymed.nlm.nih.gov>. Accessed December 30, 2021.

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

Buphenyl (sodium phenylbutyrate) tablet and powder product information, revised by Horizon Therapeutics USA, Inc. 03-2021. Available at DailyMed <http://dailymed.nlm.nih.gov>. Accessed December 30, 2021.

Sodium phenylbutyrate powder product information, revised by Par Pharmaceutical, Inc. 06-2017. Available at DailyMed <http://dailymed.nlm.nih.gov>. Accessed December 30, 2021.

Sodium phenylbutyrate tablet product information, revised by Par Pharmaceutical, Inc. 06-2017. Available at DailyMed <http://dailymed.nlm.nih.gov>. Accessed December 30, 2021.

Sodium phenylacetate and sodium benzoate Injection product information, revised by Ailex Pharmaceuticals, LLC. 02-2016. Available at DailyMed <http://dailymed.nlm.nih.gov>. Accessed December 30, 2021.

Lee B. Urea cycle disorders: Management. In: UpToDate, Hahn S, TePas E (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at <http://uptodate.com>. Topic last updated August 06,2021. Accessed December 30, 2021.