BlueCross BlueShield of Arizona
An Independent Licensee of the Blue Cross and Blue Shield Association

PHARMACY COVERAGE GUIDELINES	**ORIGINAL EFFECTIVE DATE: 7/16/15**
SECTION: DRUGS	**LAST REVIEW DATE: 3/15/18**
	LAST CRITERIA REVISION DATE: 3/15/18
	ARCHIVE DATE:

CARBAGLU® (carglumic acid) oral tablet
RAVICTI® (glycerol phenylbutyrate) oral liquid

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.

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.

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) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

CARBAGLU® (carglumic acid) oral tablet
RAVICTI® (glycerol phenylbutyrate) oral liquid (cont.)

Description:

Carbaglu (carglumic acid) 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 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. 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 in a tablet and powder formulations (brand Buphenyl) or a generic oral powder formulation. It is FDA approved as adjunctive therapy in the chronic management of patients with UCD involving deficiencies of carbamylphosphate 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):

- 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

CARBAGLU® (carglumic acid) oral tablet
RAVICTI® (glycerol phenylbutyrate) oral liquid (cont.)

- 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 from 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:

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 (Arginiosuccinic Aciduria)
AG or ARG1 or ARGD – Arginase deficiency
ORNT1 - Ornathine translocase or ornithine transporter mitochondrial 1 deficiency
CITRIN - Aspartate glutamate translocation deficiency

Carbaglu (carglumic acid)

Medication class:
Antidote, Metabolic Alkalosis Agent, Urea Cycle Disorder Treatment

FDA-approved indication(s):
- Adjunctive therapy for the treatment of acute hyperammonemia due to the deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS).
  - During acute episodes, other ammonia lowering therapies such as alternative pathway medications, hemodialysis, and dietary protein restriction is recommended
- Maintenance therapy for the treatment of chronic hyperammonemia due to the deficiency of NAGS
  - Other ammonia lowering therapies and dietary protein restriction may be needed based on plasma ammonia levels

Recommended Dose:
- Initial dose for acute hyperammonemia:
  - Dose range as adjunctive therapy for acute hyperammonemia is 100-250mg/kg/day
  - Divide the total daily dose into 2-4 doses to be given immediately before meals or feedings
  - Doses should be rounded to the nearest 100 mg
- Maintenance dose:
  - Dose range 10-100mg/kg/day
  - Divide the total daily dose into 2-4 doses to be given immediately before meals or feedings
  - Doses should be rounded to the nearest 100 mg
  - Adjust the dose to maintain normal plasma ammonia level within the normal range for the patient's age, taking into account their clinical condition (nutritional requirements, protein intake, growth parameters, etc.)

Maximum dosage
- Not stated

Available Dosage Forms:
- 200 mg scored tablets for oral suspension in bottles of 5 tablets and 60 tablets

Warnings, Precautions, and other Clinical Information:
- Woman is breast feeding an infant or child should stop breast feeding
- Carbaglu is not labeled for use in treatment of hyperammonemia due to deficiency of hepatic enzymes other than N-acetylglutamate synthase (NAGS), amyotrophic lateral sclerosis, anemia, including sickle cell anemia, cancer, homozygous beta thalassemia, cirrhosis, hepatic encephalopathy, treatment of acute or chronic hyperammonemia from other diseases, cystic fibrosis, and progressive familial intrahepatic cholestasis (a.k.a. Byler disease)

CARBAGLU® (carglumic acid) oral tablet
RAVICTI® (glycerol phenylbutyrate) oral liquid (cont.)

Criteria:
Carbaglu (carglumic acid)

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

  1. A confirmed diagnosis of urea cycle disorder with hyperammonemia due to deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS) is **ONE** of the following:
     - Adjunctive therapy for the treatment of acute hyperammonemia
     - Maintenance therapy for the treatment of chronic hyperammonemia
  2. Individual has failure, intolerance or contraindication to the following:
     - **For acute hyperammonemia:** sodium benzoate/sodium phenylacetate injection
     - **For chronic hyperammonemia:** generic sodium phenylbutyrate oral powder

  Initial approval duration: 12 months

- **Criteria for continuation of coverage (renewal request):** Carbaglu (carglumic acid) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Individual's condition responded while on therapy
     - Response is defined as:
       - Plasma ammonia levels are within the normal range for the patient's age
  2. Individual has been adherent with the medication and dietary protein restriction

  Renewal duration: 12 months

Ravicti (glycerol phenylbutyrate)

Medication class:
Urea Cycle Disorder Treatment Agent

FDA-approved indication(s):
- Chronic management of patients 2 months and older with urea cycle disorders (UCDs) who cannot be managed by dietary protein restriction and/or amino acid supplementation alone
  - It must be used with dietary protein restriction and, in some cases, dietary supplements (e.g., essential amino acids, arginine, citrulline, protein-free calorie supplements).

CARBAGLU® (carglumic acid) oral tablet
RAVICTI® (glycerol phenylbutyrate) oral liquid (cont.)

Limitations of use:
- Ravicti is not indicated for treatment of acute hyperammonemia in patients with UCDs.
- Safety and efficacy for treatment of N-acetylglutamate synthase (NAGS) deficiency has not been established

Recommended Dose:
- Recommended dosage range is 4.5-11.2 mL/m²/day (5-12.4 g/m²/day)
- For patients with some residual enzyme activity who are not adequately controlled with dietary restriction, recommended starting dose is 4.5 mL/ m²/day
    - For 2 years of age and older:
        - For patients 2 years and older, give Ravicti in 3 equally divided dosages, rounded up to nearest 0.5 mL
    - For 2 months to less than 2 years of age:
        - For patients 2 months to less than 2 years of age, give Ravicti in 3 or more equally divided dosages, rounded up to nearest 0.1 mL
- Switching From Sodium Phenylbutyrate to RAVICTI:
    - Daily dosage of Ravicti (mL) = daily dosage of sodium phenylbutyrate tablets (g) X 0.86.
    - Daily dosage of Ravicti (mL) = daily dosage of sodium phenylbutyrate powder (g) X 0.81.

Maximum dosage
- 17.5 mL per day

Available Dosage Forms:
- 1.1 g/mL in a 25 mL bottle in a carton with 1 bottle or a carton with 4 bottles

Warnings, Precautions, and other Clinical Information:
- Use of corticosteroids may cause protein breakdown and increase ammonia levels
- Use with haloperidol and valproic acid may induce hyperammonemia
- Probenecid may inhibit renal excretion of Ravicti metabolites
- The safety and efficacy of Ravicti in patients with renal impairment are unknown
- No studies have been done in patients with UCDs and hepatic impairment
- Dosing for patients with moderate to severe hepatic impairment should be started at the lower end of the recommended dosing range
- Pancreatic lipases may be required for intestinal hydrolysis of Ravicti to allow release of phenylbutyrate from glycerol and then subsequent formation of the active moiety, phenylacetate
- Pancreatic insufficiency or intestinal disease resulting in fat malabsorption may result in reduced or absent digestion of Ravicti and absorption of phenylbutyrate and reduced control of plasma ammonia
- Woman is breast feeding an infant or child should stop breast feeding
- Ravicti is not labeled for use in treatment of acute hyperammonemia in patients with UCDs, amyotrophic lateral sclerosis, anemia, including sickle cell anemia, cancer, homozygous beta thalassemia, cirrhosis, hepatic encephalopathy, treatment of acute or chronic hyperammonemia from other diseases, cystic fibrosis, & progressive familial intrahepatic cholestasis (a.k.a. Byler disease)

CARBAGLU® (carglumic acid) oral tablet
RAVICTI® (glycerol phenylbutyrate) oral liquid (cont.)

Criteria:
Ravicti (glycerol phenylbutyrate)

- **Criteria for initial therapy**: Ravicti (glycerol phenylbutyrate) is considered ***medically necessary*** when **ALL** of the following criteria are met:

  1. Individual is 2 months of age or older
  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. Dietary protein restriction and/or amino acid supplementation alone have not been effective
  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, intolerance or contraindication to generic sodium phenylbutyrate oral powder
  6. There are **NO** contraindications:
     - Contraindications include:
       - Individual < 2 months of age
       - Known hypersensitivity to phenylbutyrate

  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's condition responded while on therapy
     - Response is defined as:
       - Plasma ammonia levels are within the normal range for the patient's age
  2. 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)
  3. Individual has not developed any contraindications or other exclusions to its continued use
  4. There are no significant interacting drugs

  Renewal duration: 12 months

CARBAGLU® (carglumic acid) oral tablet
RAVICTI® (glycerol phenylbutyrate) oral liquid (cont.)

Resources:

Ravicti. Package Insert. Reference ID 3530007. Revised by manufacturer June 2014. Accessed 06-02-15.

Ravicti. Package Insert. Revised by manufacturer September 2016. Accessed 02-23-17.

Ravicti. Package Insert. Revised by manufacturer April 2017. Accessed 02-16-18.

Carbaglu. Package Insert. Revised by manufacturer April 2015. Accessed 01-26-2016.

Carbaglu. Package Insert. Revised by manufacturer November 2015. Accessed 02-23-17.

Carbaglu. Package Insert. Revised by manufacturer November 2017. Accessed 02-16-18.

UpToDate: Urea cycle disorders: Management. Current through Jan 2018. https://www-uptodate-com.mwu.idm.oclc.org/contents/urea-cycle-disorders-management?source=see_link

UpToDate: Inborn errors of metabolism: Classification. Current through Jan 2018. https://www-uptodate-com.mwu.idm.oclc.org/contents/inborn-errors-of-metabolism-classification?source=see_link

UpToDate: Urea cycle disorders: Clinical features and diagnosis. Current through Jan 2018. https://www-uptodate-com.mwu.idm.oclc.org/contents/urea-cycle-disorders-clinical-features-and-diagnosis?search=hyperammonemia&source=search_result&selectedTitle=1~118&usage_type=default&display_rank=1

Haberle J, Boddaert N, Burlina A, et al.: Suggested guidelines for the diagnosis and management of urea cycle disorders. Orphanet J Rare Diseases 2012 May 29; 7:32. http://www.ojrd.com/content/7/1/32

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Fax completed prior authorization request form to 602-864-3126 or email to pharmacyprecert@azblue.com.
Call 866-325-1794 to check the status of a request.
All requested data must be provided. **Incomplete forms or forms without the chart notes will be returned.**
Pharmacy Coverage Guidelines are available at www.azblue.com/pharmacy.

Pharmacy Prior Authorization Request Form

Do not copy for future use. Forms are updated frequently.
REQUIRED: Office notes, labs, and medical testing relevant to the request that show medical justification are required.

Member Information

Member Name (first & last):	Date of Birth:	Gender:	BCBSAZ ID#:
Address:	City:	State:	Zip Code:

Prescribing Provider Information

Provider Name (first & last):	Specialty:	NPI#:	DEA#:
Office Address:	City:	State:	Zip Code:
Office Contact:	Office Phone:	Office Fax:	

Dispensing Pharmacy Information

Pharmacy Name:	Pharmacy Phone:	Pharmacy Fax:

Requested Medication Information

Medication Name:	Strength:	Dosage Form:
Directions for Use:	Quantity: / Refills:	Duration of Therapy/Use:

☐ Check if requesting **brand** only ☐ Check if requesting **generic**

☐ Check if requesting continuation of therapy (prior authorization approved by BCBSAZ expired)

Turn-Around Time For Review

☐ Standard ☐ Urgent. Sign here: _____ ☐ Exigent (requires prescriber to include a written statement)

Clinical Information

1. **What is the diagnosis? Please specify below.**

   ICD-10 Code: _____ **Diagnosis Description:** _____

2. ☐ Yes ☐ No **Was this medication started on a recent hospital discharge or emergency room visit?**

3. ☐ Yes ☐ No **There is absence of ALL contraindications.**

4. **What medication(s) has the individual tried and failed for this diagnosis? Please specify below.**
Important note: Samples provided by the provider are not accepted as continuation of therapy or as an adequate trial and failure.

Medication Name, Strength, Frequency	Dates started and stopped or Approximate Duration	Describe response, reason for failure, or allergy

5. **Are there any supporting labs or test results? Please specify below.**

Date	Test	Value

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Pharmacy Prior Authorization Request Form

6. Is there any additional information the prescribing provider feels is important to this review? Please specify below.
For example, explain the negative impact on medical condition, safety issue, reason formulary agent is not suitable to a specific medical condition, expected adverse clinical outcome from use of formulary agent, or reason different dosage form or dose is needed.

Signature affirms that information given on this form is true and accurate and reflects office notes

Prescribing Provider's Signature: Date:

Please note: Some medications may require completion of a drug-specific request form.

Incomplete forms or forms without the chart notes will be returned.

Office notes, labs, and medical testing relevant to the request that show medical justification are required.