Drug Coverage Policy

Effective Date.....5/1/2026
Coverage Policy Number.....IP0438
Policy Title.....Carglumic Acid for Individual and Family Plans

Metabolic Disorders – Carglumic Acid for Individual and Family Plans

- Carbaglu® (carglumic acid tablets for oral suspension – Recordati Rare Diseases, generic)

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

OVERVIEW

Carglumic acid, a carbamoyl phosphate synthetase 1 (CPS 1) activator, is indicated as adjunct therapy to standard of care for the following uses:1

- N-acteylglutamate synthase (NAGS) deficiency with acute or chronic hyperammonemia.
- Propionic acidemia or methylmalonic acidemia with acute hyperammonemia.

For NAGS deficiency, the prescribing information notes that treatment with carglumic acid should be initiated as soon as the disorder is suspected, which may be as soon as birth.1

For acute hyperammonemia due to propionic acidemia or methylmalonic acidemia, carglumic acid is indicated as adjunctive therapy for acute treatment.1 In this setting, carglumic acid should be continued until the patient's ammonia level is < 50 micromol/L and for a maximum duration of 7 days.

Disease Overview

NAGS Deficiency

Carglumic acid is a synthetic analog of N-acetylglutamate, which activates CPS 1, the first reaction in the urea cycle.1 The function of the urea cycle is to convert ammonia into urea for urinary excretion. In the case of NAGS deficiency, N-acetylglutamate is not sufficiently produced due to lack of the NAGS enzyme.2 NAGS deficiency is the rarest urea cycle disorder with an estimated incidence of less than 1:2,000,000 live births. Age of diagnosis can vary from neonatal to adulthood; based on literature review, most cases present in the early neonatal period. Therefore, newborn screening is of limited value as patients are likely to be symptomatic before screening results are available. Common presenting features include poor feeding, vomiting, lethargy, decreased consciousness, seizures, and hypotonia. Laboratory abnormalities include hyperammonemia which can lead to significant morbidity and mortality in severe cases. Genetic testing is required to confirm the diagnosis; however, given the delays involved with genetic testing, it has been suggested that a therapeutic trial of carglumic acid should be initiated for any patient with unexplained hyperammonemia.

Propionic Acidemia and Methylmalonic Acidemia

In propionic and methylmalonic acidemias, other enzymatic defects result in accumulation of propionyl-coenzyme A (CoA), which acts as a competitive inhibitor for NAGS.3,4 The incidence of propionic acidemia is 1:100,000 to 1:150,000, and the incidence of methylmalonic acidemia is 1:50,000.3 According to guidelines for management of propionic acidemia and methylmalonic acidemia (2021), these disorders should be considered in any newborn/child (critically ill or not) with unexplained metabolic acidosis (with elevated anion gap); elevated lactate; hyperammonemia; leukopenia, thrombocytopenia, anemia; and/or urine ketone bodies. If ammonia is increased, further metabolic investigations should be performed immediately but specific treatment must not be delayed. Carglumic acid is supported as part of the initial management plan for symptomatic hyperammonemia both in patients with known propionic/methylmalonic acidemia and in undiagnosed patients. Other elements of initial management include cessation of protein intake, use of intravenous glucose and insulin, and other medications such as carnitine and vitamin B12. Extracorporeal detoxification (i.e., dialysis) may be used in some cases, particularly for extremely elevated ammonia levels.

Coverage Policy

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of carglumic acid. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with carglumic acid as well as the monitoring required for adverse events and long-term efficacy, approval requires carglumic acid to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: Documentation is required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory tests,

claims records, prescription receipts and/or other information. All documentation must include patient-specific identifying information.

Carglumic acid is considered medically necessary when ONE of the following is met:

FDA-Approved Indications

1. **N-Acetylglutamate Synthase Deficiency with Hyperammonemia.** Approve for the duration noted below if the patient meets **ALL** of the following criteria (A, B, C and D):
   A. The diagnosis is supported by ONE of the following (i or ii):
      i. Approve for 1 year if genetic testing confirmed a mutation leading to N-acetylglutamine synthase deficiency **[documentation required]**; OR
      ii. Approve for 3 months if the patient has hyperammonemia diagnosed with an ammonia level above the upper limit of the normal reference range for the reporting laboratory **[documentation required]**; AND
      Note: Ammonia level reference ranges are dependent upon patient's age.
   B. The medication is prescribed in conjunction with a protein-restricted diet; AND
   C. The medication is prescribed by or in consultation with a metabolic disease specialist (or specialist who focuses on the treatment of metabolic diseases); AND
   D. Preferred product criteria is met for the product(s) as listed in the below table(s).

2. **Propionic Acidemia or Methylmalonic Acidemia with Hyperammonemia, Acute Treatment.** Approve for 7 days if the patient meets **ALL** of the following criteria (A, B, C and D):
   A. Patient's plasma ammonia level is ≥50 micromol/L **[documentation required]**; AND
   B. Medication is prescribed in conjunction with other ammonia-lowering therapies; AND
   C. Medication is prescribed by or in consultation with a metabolic disease specialist (or specialist who focuses on the treatment of metabolic diseases); AND
   D. Preferred product criteria is met for the product(s) as listed in the below table(s).

Individual and Family Plans:

Product	Criteria
Carbaglu (carglumic acid)	Patient has tried **carglumic acid tablets for oral suspension** (the bioequivalent generic product) AND cannot take due to a formulation difference in the inactive ingredient(s) [e.g. difference in dyes, fillers, preservatives] between the Brand and the bioequivalent generic product which would result in a significant allergy or serious adverse reaction.

Conditions Not Covered

Carglumic acid for any other use is considered not medically necessary, including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

1. **Propionic Acidemia or Methylmalonic Acidemia with Hyperammonemia, Maintenance**. Chronic use of carbaglumic acid (beyond 7 days) for propionic acidemia or methylmalonic acidemia is not indicated.[1] There is no clinical evidence for long-term use of carbaglumic acid in propionic acidemia or methylmalonic acidemia.[3]

Receipt of sample product does not satisfy any criteria requirements for coverage.

References

1. Carbaglu® tablets [prescribing information]. Lebanon, NJ: Recordati Rare Diseases; January 2024.
2. Kenneson A, Singh RH. Presentation and management of N-acetylglutamate synthase deficiency: a review of the literature. *Orphanet J Rare Dis*. 2020;15(1):279.
3. Forny P, Hörster F, Ballhausen D, et al. Guidelines for the diagnosis and management of methylmalonic acidaemia and propionic acidaemia: First revision. *J Inherit Metab Dis*. 2021 May;44(3):566-592.
4. Haijes HA, van Hasselt PM, Jans JJM, Verhoeven-Duif NM. Pathophysiology of propionic and methylmalonic acidemias. Part 2: Treatment strategies. *J Inherit Metab Dis*. 2019 Sep;42(5):745-761.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Revision	No criteria changes.	5/1/2025
Annual Revision	**Policy Title**: The policy name was changed from "Carglumic Acid" to as listed. **Updated** terminology was standardized throughout the policy to align references from "Carbaglu" to "carglumic acid". **N-Acetylglutamate Synthase Deficiency with Hyperammonemia**. "N-acetylglutamate synthase (NAGS) deficiency" language was clarified, with emphasis on consistent clinical terminology.**Updated** criterion 1A: • **Clarified** approval pathways to distinguish genetic confirmation versus biochemical evidence of hyperammonemia. • **Added** documentation required for: ○ Genetic testing confirming a pathogenic variant leading to NAGS deficiency. ○ Laboratory confirmation of hyperammonemia (ammonia level above the upper limit of normal). **Clarified** duration language: • 1-year approval tied to genetic confirmation. • 3-month approval tied to hyperammonemia diagnosis. **Added** a "Note" indicating that normal ammonia reference ranges are age-dependent. **Clarified** criterion 2 approval duration: acute treatment is now explicitly limited to 7 days when criteria are met; criteria continue to require that all listed criteria (A, B, C, and D) are met, with less redundant diagnostic phrasing.	5/1/2026

	Preferred Product Criteria: **Added** examples of formulation differences. Minor formatting and wording clarifications were made within the Coverage Policy Criteria and Preferred Product Criteria language.	

The policy effective date is in force until updated or retired.