PRIOR AUTHORIZATION POLICY

POLICY: Metabolic Disorders – Carbaglu Prior Authorization Policy
- Carbaglu® (carglumic acid tablets for oral suspension – Recordati Rare Diseases)

REVIEW DATE: 02/05/2025

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 AND HAVE DISCRETION IN MAKING INDIVIDUAL COVERAGE DETERMINATIONS. 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.

CIGNA NATIONAL FORMULARY COVERAGE:

OVERVIEW

Carbaglu, 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 Carbaglu 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, Carbaglu is indicated as adjunctive therapy for acute treatment.[1] In this setting, Carbaglu 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

Carbaglu 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 Carbaglu 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. Carbaglu 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 B_{12}. Extracorporeal detoxification (i.e., dialysis) may be used in some cases, particularly for extremely elevated ammonia levels.

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Carbaglu. 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 Carbaglu as well as the monitoring required for adverse events and long-term efficacy, approval requires Carbaglu to be prescribed by or in consultation with a physician who specializes in the condition being treated.

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is(are) covered as medically necessary when the following criteria is(are) met for FDA-approved indication(s) or other uses with supportive evidence (if applicable):

FDA-Approved Indications

1. **N-Acetylglutamate Synthase Deficiency with Hyperammonemia.** Approve for the duration noted below if the patient meets ALL of the following (A, B, and C):
   A) According to the prescriber, 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-acetylglutamate synthase deficiency; 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; 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).

2. **Propionic Acidemia or Methylmalonic Acidemia with Hyperammonemia, Acute Treatment.** Approve for 7 days if the patient meets ALL of the following (A, B, and C):
   A) Patient's plasma ammonia level is ≥ 50 micromol/L; AND
   B) The medication is prescribed in conjunction with other ammonia-lowering therapies; AND
   Note: Examples of other ammonia-lowering therapies include intravenous glucose, insulin, L-carnitine, protein restriction, and dialysis.
   C) The medication is prescribed by or in consultation with a metabolic disease specialist (or specialist who focuses on the treatment of metabolic diseases).

CONDITIONS NOT COVERED

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

is(are) considered experimental, investigational, or unproven for ANY other use(s) 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 Carbaglu (beyond 7 days) for propionic acidemia or methylmalonic acidemia is not indicated.[1] There is no clinical evidence for long-term use of Carbaglu in propionic acidemia or methylmalonic acidemia.[3]

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.

HISTORY

Type of Revisio	Summary of Changes	Review Date
Annual Revision	No criteria changes.	01/18/2023
Annual Revision	No criteria changes.	01/17/2024
Annual Revision	No criteria changes.	02/05/2025