carglumic acid (Carbaglu®)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO211

Description

Carglumic acid (Carbaglu) is an orally administered carbamoyl phosphate synthetase 1 (CPS 1) activator.

Length of Authorization

- Initial:
  - i. Acute hyperammonemia due to NAGS deficiency: 12 months
  - ii. Chronic hyperammonemia due to NAGS deficiency: 12 months
  - iii. Acute hyperammonemia due PA or MMA: 7 days
- Renewal:
  - i. Acute hyperammonemia due to NAGS deficiency: No renewal
  - ii. Chronic hyperammonemia due to NAGS deficiency: 12 months
  - iii. Acute hyperammonemia due to PA or MMA: No renewal

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
carglumic acid (generic Carbaglu)	Adjunctive therapy for acute hyperammonemia due to NAGS deficiency	200 mg tablet	250 mg/kg/day
	Maintenance therapy for chronic hyperammonemia due to NAGS deficiency		100 mg/kg/day
	Adjunctive therapy for acute hyperammonemia due to PA or MMA		≤15 kg: 150 mg/kg/day >15 kg: 3.3 g/m^2/day
carglumic acid (Carbaglu)	Adjunctive therapy for acute hyperammonemia due to NAGS deficiency	200 mg tablet	250 mg/kg/day
	Maintenance therapy for chronic hyperammonemia due to NAGS deficiency		100 mg/kg/day
	Adjunctive therapy for acute hyperammonemia due to PA or MMA		≤15 kg: 150 mg/kg/day >15 kg: 3.3 g/m^2/day

Initial Evaluation

I. **Carglumic acid (Carbaglu)** may be considered medically necessary when the following criteria are met:
   A. Medication is prescribed by, or in consultation with, a metabolic disease specialist; **AND**
   B. Documentation of member's weight within the past three months; **AND**
   C. Documentation of baseline ammonia level indicating member has hyperammonemia (ammonia level is above the upper limit of normal based on member's age); **AND**
   D. Treatment with generic carglumic acid (generic for Carbaglu) has been ineffective, contraindicated, or not tolerated; **AND**
   E. A diagnosis of one of the following:
      1. **Hepatic enzyme N-acetylglutamate synthase (NAGS) deficiency**; **AND**
         i. Diagnosis is confirmed by mutation of the *NAGS* gene via molecular genetic testing; **AND**
         ii. The request is for acute treatment of hyperammonemia; **OR**
         iii. The request is for chronic treatment of hyperammonemia; **OR**
      2. **Propionic acidemia (PA) or methylmalonic acidemia (MMA); AND**
         i. The request is for acute management of hyperammonemia; **AND**
         ii. Diagnosis is confirmed by enzymatic, biochemical, or genetic testing; **AND**
         iii. Documentation of member's height or body surface area (BSA) within the past three months if member's weight is above 15 kg

II. Carglumic acid (Carbaglu) is considered investigational when used for all other conditions, including but not limited to:
   A. Chronic treatment (use beyond 7 days) of hyperammonemia due to MMA/PA
   B. Carbamoyl-Phosphate Synthase I Deficiency
   C. Ornithine Carbamoyltransferase Deficiency
   D. Other Urea Cycle disorders

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. The request is for **chronic hyperammonemia due to NAGS deficiency**; **AND**
IV. Documentation of member's weight within the past three months; **AND**

V. Member has exhibited a reduction from baseline in plasma ammonia levels; **OR**
   A. Member has maintained a plasma ammonia level within normal range for member's age; **AND**

V. Treatment with generic carglumic acid (generic for Carbaglu) has been ineffective, contraindicated, or not tolerated.

Supporting Evidence

I. NAGS deficiency is a rare autosomal recessive genetic disorder caused by mutations of the NAGS gene leading to complete or partial deficiency in the enzyme N-acetylglutamate synthetase (NAGS). The hepatic enzyme NAGS is necessary to break down nitrogen in the body. NAGS deficiency leads to accumulation of nitrogen in the form of ammonia in the blood (hyperammonemia). In most cases, onset of symptoms occurs at, or shortly following, birth (neonatal period); however, some individuals with NAGS deficiency may not exhibit symptoms until later during infancy, childhood, or even adulthood due to a partial deficiency of the NAGS enzyme. Symptoms of NAGS deficiency may include failure to thrive, poor growth, avoidance of protein from the diet, ataxia, lethargy, vomiting, and/or hypotonia. Severe manifestations include hyperammonemic coma and life-threatening complications.

II. Because NAGS deficiency is classified as an orphan disease and shares many symptoms with five other rare urea cycle disorders that result in hyperammonemia, diagnosis should be confirmed by genetic testing to verify the mutation in the *NAGS* gene. Furthermore, disease management should be by, or in consultation with, a physician who specializes in metabolic disorders.

III. Blood ammonia levels should be drawn to ensure the patient has hyperammonemia. Normal blood ammonia levels based on age are outline in the table below:

Age	Normal blood ammonia ranges
0 to 10 days (enzymatic)	170 - 341 mcg/dL
Infants and toddlers [10 days to 2 years] (enzymatic)	68 - 136 mcg/dL
Children [2 years and older]	19 - 60 mcg/dL
Adults	10 - 80 mcg/dL

IV. According to the FDA label, initial dosing for pediatric and adults with acute hyperammonemia is 100mg/kg/day to 250mg/kg/day. Maintenance for chronic hyperammonemia for pediatrics and adults is 10mg/kg/day to 100mg/kg/day. Dosage should be titrated and/or adjusted to target normal plasma ammonia level for age (referenced above).

V. The safety and efficacy of carglumic acid (Carbaglu) in the treatment of hyperammonemia due to NAGS deficiency was evaluated in a retrospective review of 23 NAGS deficiencient patients (including newborns, pediatrics, and adults) over a median period of 7.9 years (range 0.6 to 20.8 years). Due to the retrospective, unblinded, and uncontrolled nature of this review, formal

statistical analyses of the data was not conducted; however, short term efficacy was evaluated using mean and median change in plasma ammonia levels from baseline to days one to three, while persistence of efficacy was evaluated using long-term mean and median change in plasma ammonia level. Thirteen out of 23 patients who received carglumic acid (Carbaglu), had documented ammonia levels prior to treatment initiation and after long-term treatment. All 13 patients had abnormally elevated ammonia levels at baseline with an overall mean baseline plasma ammonia level of 271 micromol/L. For acute treatment, normal ammonia levels were attained on day three of treatment. Long-term efficacy was measured using the last reported plasma ammonia level for each patient (median length of treatment was six years; range one to 16 years). The mean and median ammonia levels were 23 micromol/L and 24 micromol/L, respectively, after a mean treatment duration of eight years.

VI. For the treatment of acute hyperammonemia due to NAGS deficiency the length of authorization is limited to 12 months. In clinical studies, doses from acute to maintenance treatment of hyperammonemia due to NAGS deficiency were reduced over time. Dose reduction to achieve a maintenance dose was undertaken within days of initiation and took anywhere from one day to 15 days for a dose reduction to be performed in majority of patents (16 of 22 patients). In five patients, it took anywhere from one month to 10 months for the dose reduction process. Thus, it is expected that 12 months initial authorization would be sufficient to allow for titration from acute to maintence dosing and renewal would not be necessary.

VII. Methylmalonic and propionic acidemia (MMA/PA) are autosomal recessive genetic disorders characterized by accumulation of propionic acid and/or methylmalonic acid due to deficiency of methylmalonyl-CoA mutase (MUT) or propionyl-CoA carboxylase (PCC). Patients may present in the first days to weeks of life with acute deterioration of their general clinical condition, metabolic acidosis and hyperammonemia, progressing to coma and death, if untreated. Late-onset cases of MMA and PA may present at any age with a more heterogeneous clinical symptoms. Prognosis is strongly influenced by the duration of coma and peak blood ammonia concentrations and immediate treatment in consultation with a metabolic disease specialist is required. For the treatment of acute hyperammonemia due to MMA or PA, carglumic acid (Carbaglu) is expected to be administered in an inpatient setting due to the severity of presenting symptoms, need for immediate treatment and frequent monitoring.

VIII. Length of authorization is limited to seven days of treatment which is consistent with how the drug was studied in clinical trials. Acute treatment with carglumic acid (Carbaglu) should be continued until ammonia level is less than 50 micromol/L or for a maximum duration of seven days to attain a normal blood ammonia, whichever is shorter. Efficacy and safety of treating a hyperammonemic episode beyond seven days has not been established. Patients requiring re-treatment with Carglumic acid (Carbaglu) for a second hyperammonemic episode and beyond must meet initial criteria.

IX. Determination of organic acids in urine and the acylcarnitine profile in blood are the most commonly used investigations to detect MMA and PA. Enzymatic studies and/or molecular

genetic analyses should be performed to confirm diagnosis. This is ideally performed in specialized laboratories.

X. Carglumic acid (Carbaglu) was studied in one randomized, double-blind, placebo-controlled, multicenter clinical trial to determine efficacy and safety in patients with hyperammonemia due to PA and MMA. Patients were randomized 1:1 to receive carglumic acid (Carbaglu) or placebo for 7 days or until hospital discharge, which ever occurred earlier. A total of 24 patients were evaluated (PA=15, MMA=9) with median age of 8 years (range 4 days to 29 years), and all receiving standard of care, including combination of protein restriction, intravenous glucose, insulin, and/or L-carnitine. Carglumic acid (Carbaglu) was dosed at 150mg/kg/day for patients ≤15 kg or 3.3g/m^2/day for patients >15 kg administered by NG tube, G-tube, or oral syringe. Efficacy was determined based on 90 hyperammonemic episodes (42 treated with carglumic acid (Carbaglu) and 48 with placebo). Eligible hyperammonemic episodes were defined as admission to the hospital with a plasma ammonia level ≥70 µmol/L. The primary endpoint was the time from the first dose of drug to the earlier of plasma ammonia level ≤50 µmol/L (normal range) or hospital discharge. The median time to reach the primary endpoint was 1.5 days in the carglumic acid (Carbaglu) arm compared to 2 days in the placebo arm (0.5 day; 95% CI: -1.2,0.1). Throughout the first three days of treatment, a higher proportion of carglumic acid (Carbaglu) treated episodes reached the primary endpoint compared to placebo-treated episodes. At least one adverse reaction was reported during the course of hyperammonemic episodes in 42.2% of hyperammonemic episodes. The most common adverse reactions (≥5%) during hyperammonemic episodes were neutropenia, anemia, vomiting, electrolyte imbalance, decreased appetite, hypoglycemia, lethargy/stupor, encephalopathy, and pancreatitis/increased lipase.

Investigational or Not Medically Necessary Uses

I. Carglumic acid (Carbaglu) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Chronic treatment (use beyond 7 days) of hyperammonemia due to MMA/PA
      i. Carglumic acid (Carbaglu) is not FDA approved or supported by current clinical guidelines for long-term management of PA or MMA. One low evidence grade, randomized, parallel-group, open-label clinical trial studied carglumic acid (Carbaglu) for long-term treatment of PA and MMA against standard of care. Long term effectiveness was evaluated as a reduction in the number of ER admissions due to hyperammonemia. There was a 51% reduction (p=0.0095) in the number of ER admissions during the two-year observation period. No serious safety concerns reported. Additional randomized clinical trials with clinically meaningful outcomes are required to confirm signals of efficacy.
   B. Carbamoyl-Phosphate Synthase I Deficiency

C. Ornithine Carbamoyltransferase Deficiency
D. Other Urea Cycle disorders

References

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Policy Implementation/Update:

Action and Summary of Changes	Date
Added new indication of acute treatment of hyperammonemia due to PA or MMA to initial criteria; changed initial authorization for acute hyperammonemia due to NAGS deficiency from 3 to 12 months; changed renewal authorization for acute hyperammonemia due to NAGS deficiency from 12 months to no renewal; updated supporting evidence section and experimental and not medically necessary sections.	05/2022
Added criteria of a trial and failure of generic Carbaglu prior to using branded product	12/2021
Transitioned criteria to policy format; Added requirement for weight documentation and supporting evidence section.	12/2020
Criteria created	12/2015