

## PRIOR AUTHORIZATION POLICY

- POLICY:** Metabolic Disorders – Carbaglu Prior Authorization Policy
- Carbaglu (carglumic acid tablets for oral suspension – Orphan Europe, SARL/Recordati Rare Diseases)

**REVIEW DATE:** 03/03/2021

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### OVERVIEW

Carbaglu, a carbamoyl phosphate synthetase 1 (CPS 1) activator, is indicated in adults and pediatric patients for the following conditions:<sup>1</sup>

- **N-acetylglutamate synthase (NAGS) deficiency** with chronic hyperammonemia or acute hyperammonemia (as adjunct therapy to standard of care).
- **Propionic acidemia or methylmalonic acidemia** with acute hyperammonemia (as adjunct therapy to standard of care).

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.<sup>1</sup>

For acute hyperammonemia due to propionic acidemia or methylmalonic acidemia, Carbaglu is indicated as adjunctive therapy for acute treatment.<sup>1</sup> 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.<sup>1</sup> 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.<sup>2</sup> 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.<sup>3,4</sup> The incidence of propionic acidemia is 1:100,000 to 1:150,000, and the incidence of methylmalonic acidemia is 1:50,000.<sup>3</sup> According to guidelines for management of propionic acidemia and methylmalonic acidemia (2014), 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

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intake, use of intravenous glucose and insulin, and other medications such as carnitine and vitamin B<sub>12</sub>. 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.

**Automation:** None.

### **RECOMMENDED AUTHORIZATION CRITERIA**

Coverage of Carbaglu is recommended in those who meet the following criteria:

#### **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, 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.  
Note: Reference ranges are dependent upon patient's age; AND
  - 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 in the treatment of metabolic diseases).
  
- 2. Propionic Acidemia or Methylmalonic Acidemia with Hyperammonemia, Acute Treatment.** Approve for 7 days if the patient meets the following criteria (A, B, and C):
  - A)** Patient's plasma ammonia level is  $\geq 50$  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 in the treatment of metabolic diseases).

### **CONDITIONS NOT RECOMMENDED FOR APPROVAL**

Coverage of Carbaglu is not recommended in the following situations:

- 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.<sup>1</sup> There is no clinical evidence for long-term use of Carbaglu in propionic acidemia or methylmalonic acidemia.<sup>3</sup>
- 2.** Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

### **REFERENCES**

1. Carbaglu® tablets [prescribing information]. Lebanon, NJ: Recordati Rare Diseases; January 2021.
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. Baumgartner MR, Hörster F, Dionisi-Vici C, et al. Proposed guidelines for the diagnosis and management of methylmalonic and propionic acidemia. *Orphanet J Rare Dis.* 2014 Sep 2;9:130.
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.