PRIOR AUTHORIZATION POLICY

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

DATE REVIEWED: 03/11/2020

OVERVIEW

Carbaglu is indicated in pediatric and adult patients, both as an adjunctive therapy for the treatment of acute hyperammonemia, and for maintenance therapy for chronic hyperammonemia, due to the deficiency of the hepatic enzyme N-acetylglutamate (NAGS). It is a synthetic structural analogue of N-acetylglutamate (NAG) thereby acting as a replacement for NAG in patients with NAGS deficiency. During acute hyperammonia, other therapies, including protein restriction, is recommended. During the maintenance therapy, concomitant use of other ammonia lowering therapies and protein restriction may be needed based on plasma ammonia levels.

Disease Overview

NAGS deficiency is one of the rarest urea cycle disorders.[2-3] NAGS is an enzyme that is located in the liver and intestine, and is essential for the function of the urea cycle. Although NAGS deficiency can be suspected based on patient/family history and high levels of ammonia in the blood, the diagnosis is confirmed by molecular genetic testing.[5] Of note, there are 12 gene mutations that have been identified resulting a NAGS deficiency. The neonatal-onset phenotype usually reflects complete absence of NAGS activity.[2-3] Symptoms result primarily from hyperammonemia. If newborns survive the acute hyperammonemic episode, they typically go on to exhibit significant developmental delays, residual neurologic impairments, and seizure disorders. The degree of neurologic impairment in urea cycle disorders has been shown to correlate with peak levels of ammonia and the duration of hyperammonemic coma. Late-onset NAGS deficiency has a variable age of onset, and the degree of residual enzyme activity is heterogeneous.

Clinical Efficacy

In the pivotal trial evaluating Carbaglu, all patients had NAGS gene mutations by DNA testing with elevation of baseline ammonia levels prior to initial dose of Carbaglu (range, 72 to 1,428 µmol/L [normal range, 5 to 50 µmol/L]).[1] By Day 3, the mean ammonia level decreased below 50 µmol/L and remained in this range with long-term treatment.

Safety

Carbaglu has a Warning/Precaution for hyperammonemia. Any episode of acute, severe symptomatic hyperammonemia should be treated as a life-threatening emergency. Treatment of severe hyperammonemia may require dialysis, preferably hemodialysis and/or hemofiltration, to reduce plasma ammonia concentration. Untreated hyperammonemia can result in brain damage and death, and prompt use of all therapies necessary to reduce plasma ammonia level is essential.

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 (NAGS) 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 (NAGS); 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).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Carbaglu has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

1. 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 [prescribing information]. Lebanon, NJ: Recordati Rare Diseases; December 2019.
2. Center for Drug Evaluation and Research (CDER). Application Number: 22-562. Medical Review. July 30, 2009. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022562s000medr.pdf. Accessed on February 25, 2020.
3. Summar ML. Urea cycle disorders overview. GeneReviews. Updated June 22, 2017. Available at: http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=ucd-overview. Accessed on February 25, 2020.
4. National Organization for Rare Disorders (NORD). N-acetylglutamate synthetase deficiency. Accessed on February 25, 2020. Available at: https://rarediseases.org/rare-diseases/n-acetylglutamate-synthetase-deficiency/.