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Coverage Policy Number **IP0438**

Carglumic Acid

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Related Coverage Resources

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. 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

This policy supports medical necessity review for carglumic acid (**Carbaglu**®) tablets for oral suspension.

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

Medical Necessity Criteria

Carglumic acid (**Carbaglu**) **is considered medically necessary when ONE of the following is met:**

1. **N-acetylglutamate Synthase (NAGS) Deficiency with Hyperammonemia.** Individual meets **ALL** of the following criteria:
   A. Documented diagnosis of NAGS deficiency with hyperammonemia is confirmed by enzymatic, biochemical or genetic analysis
   B. Medication is prescribed in conjunction with a protein-restricted diet
   C. Medication is prescribed by, or in consultation with, a metabolic disease specialist (or specialist who focuses in the treatment of metabolic diseases)

D. Non-Covered Product Criteria is met, refer to below table(s)

2. **Propionic Acidemia or Methylmalonic Acidemia with Hyperammonemia (Acute Treatment).** Individual meets **ALL** of the following criteria:
   A. Documented diagnosis of propionic acidemia or methylmalonic acidemia with hyperammonemia (acute treatment) is confirmed by enzymatic, biochemical or genetic analysis
   B. Documentation of plasma ammonia level is greater than or equal to 50 micromol/L
   C. Medication is prescribed in conjunction with other ammonia-lowering therapies
   D. Medication is prescribed by, or in consultation with, a metabolic disease specialist (or specialist who focuses in the treatment of metabolic diseases)
   E. Non-Covered Product Criteria is met, refer to below table(s)

Individual and Family Plan Non-Covered Products and Criteria:

Non-Covered Product	Criteria
Carbaglu (carglumic acid)	Documented trial of **carglumic acid tablets for oral suspension** (the bioequivalent generic product) AND cannot take due to a formulation difference in the inactive ingredient(s) which would result in a significant allergy or serious adverse reaction

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Reauthorization Criteria

Continuation of carglumic acid (Carbaglu) is considered medically necessary for NAGS deficiency with hyperammonemia when the above medical necessity criteria are met AND there is documentation of beneficial response.

Authorization Duration

Initial approval duration:
1. NAGS deficiency with hyperammonemia: up to 12 months
2. Propionic acidemia or methylmalonic acidemia with hyperammonemia (acute treatment): up to 7 days

Reauthorization approval duration:
1. NAGS deficiency with hyperammonemia: up to 12 months
2. Propionic acidemia or methylmalonic acidemia with hyperammonemia (acute treatment): not applicable for continuation beyond initial approval duration

Conditions Not Covered

Any other use is considered experimental, investigational or unproven, including the following (this list may not be all inclusive):

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]

Background

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.

DIAGNOSTIC INFORMATION:

NAGS deficiency:
Gene: *NAGS*
Enzyme: N-Acetylglutamate synthase
Biochemical findings:

- Plasma amino acids: elevated glutamine, reduced citrulline
- Urine orotic acid: normal or low

Propionic acidemia:
Genes: *PCCA* or *PCCB*
Enzyme: propionyl-CoA carboxylase (PCC)
Biochemical findings:

- Plasma acylcarnitine profile: elevated propionylcarnitine (C3)
- Urine organic acids: elevated 3-hydroxypropionate, presence of methylcitrate, tiglylglycine, propionylglycine, lactic acid

- Plasma amino acids: elevated glycine

Methylmalonic acidemia:
Genes: *MMUT, MMAA, MMAB, MCEE*, or *MMADHC*
Enzymes: methylmalonyl-CoA mutase, methylmalonyl-CoA epimerase, or adenosyl-cobalamin (cblA, cblB, or cblD-MMA; defect in transport or synthesis of this gene)
Biochemical findings:

- Plasma acylcarnitine profile: elevated propionylcarnitine (C3)
- Urine organic acids: elevated methylmalonic acid, presence of 3-hydroxypropionate, 2-methylcitrate, and tiglylglycine
- Plasma methylmalonic acid: elevated
- Plasma amino acids: elevated glycine

References

1. Carbaglu tablets [prescribing information]. Lebanon, NJ: Recordati Rare Diseases; August 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. 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.