Clinical Policy: Carglumic Acid (Carbaglu)

Reference Number: ERX.SPA.22
Effective Date: 07.01.16
Last Review Date: 05.21
Line of Business: Commercial, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Carglumic acid (Carbaglu®) is a carbamoyl phosphate synthetase 1 activator.

FDA Approved Indication(s)
Carbaglu is indicated as:

- Adjunctive therapy in pediatric and adult patients for the treatment of acute hyperammonemia due to the deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS). During acute hyperammonemic episodes concomitant administration of Carbaglu with other ammonia lowering therapies such as alternate pathway medications, hemodialysis, and dietary protein restriction are recommended.
- Maintenance therapy in pediatric and adult patients for the treatment of chronic hyperammonemia due to the deficiency of the hepatic enzyme NAGS. During maintenance therapy, the concomitant use of other ammonia lowering therapies and protein restriction may be needed based on plasma ammonia levels.
- Adjunctive therapy to standard of care in pediatric and adult patients for the treatment of acute hyperammonemia due to propionic academia (PA) or methylmalonic acidemia (MMA).

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Carbaglu is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Urea Cycle Disorder: NAGS (must meet all)**:**
1. Diagnosis of a urea cycle disorder (UCD) caused by NAGS deficiency;
2. NAGS deficiency is confirmed by enzymatic, biochemical or genetic analysis;
3. Prescribed by or in consultation with a physician experienced in treating metabolic disorders;
4. Dose does not exceed 250 mg per kg per day initially, followed by a maintenance dose of 100 mg per kg per day.

Approval duration: 6 months

B. Organic Acidemias: Propionic Acidemia, Methylmalonic Academia (must meet all):
1. Diagnosis of PA or MMA;
2. Diagnosis is confirmed by urine organic acid, genetic, or enzymatic analysis;
3. Prescribed by or in consultation with a physician experienced in treating metabolic disorders;
4. Plasma ammonia level ≥ 70 micromol/L despite standard of care treatment (e.g., intravenous hydration and nutritional support);
5. Prescribed as adjunctive therapy to standard of care;
6. Dose does not exceed one of the following (a or b):
   a. Weight ≤ 15 kg: 150 mg/kg/day for 7 days;
   b. Weight > 15 kg: 3.3 g/m^2/day for 7 days.

Approval duration: 7 days

C. Other diagnoses/indications
7. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. Urea Cycle Disorder: NAGS (must meet all)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member is responding positively to therapy;
3. If request is for a dose increase, dose does not exceed a maintenance dose of 100 mg per kg per day.

Approval duration: 12 months

B. Organic Acidemias: Propionic Acidemia, Methylmalonic Academia:
1. Re-authorization is not permitted. Members must meet the initial approval criteria.

Approval duration: Not applicable

C. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ASL: argininosuccinate lyase
ASS: argininosuccinate synthetase
CPSI: carbamoyl phosphate synthetase I
CTLN1: type I citrullinemia
FDA: Food and Drug Administration
MMA: methylmalonic acidemia
NAGS: N-acetyl glutamate synthetase
OTC: ornithine transcarbamylase
PA: propionic academia
UCD: urea cycle disorder

Appendix B: Therapeutic Alternatives

Not applicable

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): none reported
- Boxed warning(s): none reported

Appendix D: Urea Cycle Disorders

UCDs are caused by a deficiency in any of the below enzymes in the pathway that transforms nitrogen to urea:

- Carbamoyl phosphate synthetase I (CPS1) deficiency
- Ornithine transcarbamylase (OTC) deficiency
- Argininosuccinate synthetase (ASS) deficiency (also known as classic citrullinemia or type I citrullinemia, CTLN1)
- Argininosuccinate lyase (ASL) deficiency (also known as argininosuccinic aciduria)
- N-acetyl glutamate synthetase (NAGS) deficiency

- Arginase deficiency

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
NAGS	For acute hyperammonemia, initial dose of 100-250 mg/kg/day in 2-4 divided doses, then adjust to maintain normal plasma ammonia levels based on age (typically 10-100 mg/kg/day). For daily maintenance of hyperammonemia, recommended dose is 10-100 mg/kg/day in 2-4 divided doses, then titrate to normal plasma ammonia level for age.	Based on clinical response
PA, MMA	150 mg/kg/day for patients ≤ 15 kg 3.3 g/m^2/day for patients > 15 kg Divide the daily dosage into two equal doses and round up to the next multiple of 50 mg; administer each dose 12 hours apart. Continue treatment until ammonia level is less than 50 micromol/L and for a maximum duration of 7 days.	See dosing regimen

VI. Product Availability

Tablet for oral suspension: 200 mg

VII. References

1. Carbaglu Prescribing Information. Lebanon, NJ: Recordati Rare Diseases, Inc.; January 2021. Available at www.carbaglu.com. Accessed February 16, 2021.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	05.16	06.16
Dosing is not added as it is titrated based on individual plasma ammonia levels and clinical symptoms. Positive response to therapy is added to renewal criteria. List of UCD disorders is added at Appendix B. Duration of approval changed to 6 and 12 months for initial and continued approval respectively. PI updated.	04.17	05.17
1Q18 annual review: Removed requirement for confirmation that Carbaglu is prescribed to treat acute or chronic hyperammonemia as this is characteristic of the condition itself.	11.14.17	02.18
1Q 2019 annual review: no significant changes; references reviewed and updated.	10.25.18	02.19
1Q 2020 annual review: no significant changes; added dosing for maintenance hyperammonemia to section V; references reviewed and updated.	10.21.19	02.20
1Q 2021 annual review: no significant changes; added maximum initial and maintenance dose requirement; references reviewed and updated.	11.11.20	02.21
RT4: added new indication as adjunctive therapy for acute hyperammonemia due to PA or MMA.	02.16.21	05.21

Important Reminder
This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.