Clinical Policy: Carglumic Acid (Carbaglu)

Reference Number: CP.PHAR.206
Effective Date: 05.01.16
Last Review Date: 08.22
Line of Business: Commercial, HIM, Medicaid

Revision Log

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

Description

Carglumic acid is a carbamoyl phosphate synthetase 1 (CPS1) 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).
- Maintenance therapy in pediatric and adult patients for the treatment of chronic hyperammonemia due to the deficiency of the hepatic enzyme NAGS.
- Adjunctive therapy to standard of care in pediatric and adult patients for the treatment of acute hyperammonemia due to propionic acidemia (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.

It is the policy of health plans affiliated with Centene Corporation® 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:
Medicaid/HIM – 6 months
Commercial – 12 months or duration of request, whichever is less

B. Organic Acidemias: Propionic Acidemia, Methylmalonic Acidemia (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 (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Urea Cycle Disorder: NAGS (must meet all)**:**

1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
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:
Medicaid/HIM – 12 months
Commercial – 12 months or duration of request, whichever is less

B. Organic Acidemias: Propionic Acidemia, Methylmalonic Acidemia:

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. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

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 policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid, or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ASL: argininosuccinate lyase
ASS: argininosuccinate synthetase
CPS1: carbamyl phosphate synthetase 1
CTLN1: type I citrullinemia
FDA: Food and Drug Administration
MMA: methylmalonic acidemia
NAGS: N-acetyl glutamate synthetase
OTC: ornithine transcarbamylase
PA: propionic acidemia
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:

- N-acetyl glutamate synthetase (NAGS) deficiency
- Carbamyl phosphate synthetase 1 (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)
- 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. Titrate based on plasma ammonia level for patient's age and clinical symptoms. 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. For daily maintenance of hyperammonemia, recommended dose is 10-100 mg/kg/day in 2-4 divided doses. Titrate based on plasma ammonia level for patient's age and clinical symptoms. During maintenance therapy, the concomitant use of other ammonia lowering therapies and protein restriction may be needed based on plasma ammonia levels.	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. During acute hyperammonemic episodes, administer Carbaglu with other ammonia lowering therapies, such as intravenous glucose, insulin, L-carnitine, protein restriction, and dialysis.	See dosing regimen

VI. Product Availability

Tablet for oral suspension: 200 mg

VII. References

1. Carbaglu Prescribing Information. Lebanon, NJ: Recordati Rare Diseases, Inc.; August 2021. Available at www.carbaglu.com. Accessed September 13, 2021.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q18 annual review: - Added HIM line of business to criteria. - Removed requirement for confirmation that Carbaglu is prescribed to treat acute or chronic hyperammonemia as this is characteristic of the condition itself - References reviewed and updated.	11.14.17	02.18
1Q 2019 annual review: added Commercial line of business with length of benefit authorization consistent with criteria for other UCD therapies; references reviewed and updated.	10.25.18	02.19
1Q 2020 annual review: no significant changes; added dosing for maintenance hyperammonemia; references reviewed and updated.	10.21.19	02.20
1Q 2021 annual review: no significant changes; added maximum initial and maintenance dose requirement; references to HIM.PHAR.21 revised to HIM.PA.154; 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
1Q 2022 annual review: no significant changes; updated dosing in Section V; references reviewed and updated.	09.13.21	02.22
Revised approval duration for Commercial line of business from length of benefit to 12 months or duration of request, whichever is less.	04.26.22	08.22
Template changes applied to other diagnoses/indications and continued therapy section.	10.03.22	

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. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage

decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. 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. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note: For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.