Clinical Policy: Carglumic Acid (Carbaglu)

Reference Number: PA.CP.PHAR.206
Effective Date: 01/2018
Last Review Date: 01/2023

Coding Implications
Revision Log

Description
Carglumic acid is a carbamyl phosphate synthetase I (CPSI) activator.

FDA Approved Indication(s)
Carbaglu is indicated for:

- 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
It is the policy of PA Health & Wellness that carglumic acid 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. If request is for brand Carbaglu, member must use generic carglumic acid, unless contraindicated or clinically significant adverse effects are experienced;
5. 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 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. If request is for brand Carbaglu, member must use generic carglumic acid, unless contraindicated or clinically significant adverse effects are experienced;
7. 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: Refer to PA.CP.PMN.53

II. Continued Approval

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

1. Currently receiving medication via PA Health & Wellness benefit or member has previously met all initial approval criteria; or the Continuity of Care policy (PA.LTSS.PHAR.01) applies; or
2. Member is responding positively to therapy;
3. If request is for brand Carbaglu, member must use generic carglumic acid, unless contraindicated or clinically significant adverse effects are experienced;
4. 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 Acidemia:

1. Re-authorization is not permitted. Members must meet the initial approval criteria.

Approval duration: Not applicable

C. Other diagnoses/indications (1 or 2)**:**

1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy; or the Continuity of Care policy (PA.LTSS.PHAR.01) applies;

Approval duration: Duration of request or 6 months (whichever is less); or

2. Refer to PA.CP.PMN.53

III. 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): hyperammonemia, monitor during treatment as prolonged exposure can result in brain injury or death
- 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 I (CPSI) 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

IV. 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

V. Product Availability

Tablet for oral suspension: 200 mg

VI. References

1. Carbaglu Prescribing Information. Lebanon, NJ: Recordati Rare Diseases, Inc.; August 2021. Available at https://www.carbaglu.net/. Accessed October 27, 2022.

Reviews, Revisions, and Approvals	Date	Approval Date
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.	02/2018	
1Q 2019 annual review: references reviewed and updated.	01/2019	
1Q 2020 annual review: added dosing for maintenance hyperammonemia; references reviewed and updated.	01/2020	
1Q 2021 annual review: added maximum initial and maintenance dose requirement; references reviewed and updated.	01/2021	
Added new indication as adjunctive therapy for acute hyperammonemia due to PA or MMA.	04/2021	
1Q 2022 annual review: updated dosing in Section V; references reviewed and updated.	01/2022	
1Q 2023 annual review: added generic redirection for brand requests; references reviewed and updated.	01/2023	