Carbaglu (carglumic acid) Prior Authorization Program Summary

This program applies to FlexRx Closed, FlexRx Open, FocusRx, GenRx Closed, GenRx Open, Health Insurance Marketplace, and KeyRx formularies.

This is a FlexRx Standard and GenRx Standard program.

The BCBS MN Step Therapy Supplement also applies to this program for all Commercial/HIM lines of business.

POLICY REVIEW CYCLE

Effective Date	**Date of Origin**
12/1/2023	7/1/2018

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Carbaglu® (carglumic acid) Tablet for oral suspension*	Adjunctive therapy to standard of care in pediatric and adult patients for the treatment of acute hyperammonemia due to deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS) Maintenance therapy in pediatric and adult patients for the treatment of chronic hyperammonemia due to deficiency of the hepatic enzyme N-acetylglutamate synthase (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)	* generic available	1

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Urea Cycle Disorders	Urea cycle disorders (UCDs) are rare genetically inherited metabolic deficiencies that result from defects in the metabolism of waste nitrogen from the breakdown of protein and other nitrogen-containing molecules. Severe deficiency, or total absence, of any of the enzymes in the urea cycle (carbamoyl phosphate synthetase I [CPS1], ornithine transcarbamylase [OTC], argininosuccinic acid synthetase [ASS1], argininosuccinic acid lyase [ASL], arginase [ARG1]) or the cofactor producer (N-acetyl glutamate synthetase [NAGS]) results in the accumulation of ammonia (hyperammonemia) during the first few days of life. In severe disease, infants rapidly develop cerebral edema and signs of lethargy, anorexia, hyper- or hypoventilation, hypothermia, seizures, neurologic posturing, and coma whereas milder disease and the associated accumulation of ammonia may be triggered by illness or stress.(2,3,4) The most important diagnostic step in UCDs is clinical suspicion of hyperammonemia. Laboratory data useful in the diagnosis of UCD includes, but is not limited to, plasma ammonia, anion gap, and plasma glucose. A normal anion gap and normal blood glucose in the presence of a plasma ammonia concentration of 150 micromol/L (greater than 260 micrograms/dL) or higher in neonates and greater than 100 micromol/L (175 micrograms/dL) in older children and adults is indicative of UCD. The diagnosis of a specific UCD can be confirmed by genetic testing. Specifically, NAGS, OTC, and CPSI deficiencies can be confirmed by liver biopsy.(2,3,4)

	Pharmacologic therapy for acute hyperammonemia consists of initial IV administration of a combination preparation of sodium phenylacetate and sodium benzoate, ideally while the dialysis is being arranged and the diagnostic workup is under way. If chronic therapy is warranted, the patient can then be switched to nitrogen scavengers such as sodium phenylbutyrate, glycerol phenylbutyrate, and carglumic acid.(3,4,5) NAG is an essential cofactor of CPS1, the enzyme that catalyzes the first step of the urea cycle. A deficiency, or absence, of NAGS results in deficiency of NAG, leading to a defect in the urea cycle resulting in toxic ammonia accumulation.(3) Carglumic acid (Carbaglu) is a synthetic structural analog of NAG thereby removing the block in the urea cycle and facilitating ammonia detoxification and urea production. During acute hyperammonemic episodes, concomitant administration of carglumic acid with other ammonia lowering therapies, such as alternate pathway medications, hemodialysis, and dietary protein restriction, is recommended. During maintenance therapy, the concomitant use of other ammonia lowering therapies and protein restriction may be needed based on plasma ammonia levels.(1) Long term management options to prevent hyperammonemia includes dietary modification and nutritional oversight (e.g., protein restriction, limitation of alcohol intake, essential amino acid supplementation if clinically appropriate).(3,4,5) Not all adult patients who recover from a hyperammonemic episode require chronic nitrogen scavengers, but they ought to be considered since many of these patients can become brittle as time goes on.(3,4)
Organic Acidemias	Methylmalonic acidemia (MMA) and propionic acidemia (PA) are inborn errors of metabolism characterized by accumulation of methylmalonic acid or propionic acid, respectively, due to deficiency of methylmalonyl-CoA mutase (MUT) or propionyl-CoA carboxylase (PCC). MMA has an estimated incidence of ~ 1: 50,000 and PA of ~ 1:150,000.(6) Patients present either shortly after birth with acute deterioration, metabolic acidosis and hyperammonemia, or later at any age with a more heterogeneous clinical picture, leading to early death or to severe neurological handicap in many survivors. Mental outcome tends to be worse in PA and late complications include chronic kidney disease almost exclusively in MMA and cardiomyopathy mainly in PA. Except for vitamin B12 responsive forms of MMA, the outcome remains poor despite the existence of apparently effective therapy with a low protein diet and carnitine. This may be related to under recognition and delayed diagnosis due to nonspecific clinical presentation and insufficient awareness of health care professionals because of disease rarity.(6,7,8) In the classical, neonatal onset form of MMA or PA, symptoms start as early as the second day of life with acute deterioration of the general clinical condition, vomiting, dehydration, weight loss, temperature instability, neurological involvement with muscular hypo- or hypertonia, irritability, lethargy progressing to coma and seizures. At presentation, laboratory findings include severe and persistent metabolic acidosis and ketosis, elevated anion gap, and hyperammonemia.(6,7,8) One of the most severe life-threatening events in MMA and PA is hyperammonemia. The acute management differs depending on whether the cause of hyperammonemia is known or not. The differential diagnosis should include urea cycle defects and some other inherited disorders. The start of ammonia detoxification and measures to reverse catabolism must not be delayed. Therapy mirrors that for hyperammonemia due to NAGS deficiency (see section above, regarding pharmacologic therapy for acute hyperammonemia). Carglumic acid (Carbaglu) has been utilized in MMA and PA for its ability to antagonize propionyl-CoA induced hyperammonemia.(6,7,8) In a randomized, double-blind, placebo-controlled, multicenter clinical trial evaluating the efficacy of Carbaglu in the treatment of hyperammonemia in patients with PA and MMA, eligible patients had a hyperammonemic episode(s), defined as an admission to the hospital with a plasma ammonia level greater than or equal to 70 micromol/L. Patients were randomized 1:1 to receive either Carbaglu or placebo for 7 days or until hospital discharge, whichever occurred earlier. All patients received standard of care; the median patient age was 8 years (range 4 days to 29 years).

	The primary endpoint was the time from the first dose of drug to the earlier of plasma ammonia level less than or equal to 50 micromol/L (normal range) or hospital discharge. The median time to reach the primary endpoint was 1.5 days in the Carbaglu group compared to 2.0 days in the placebo group, a difference of 0.5 days (95% confidence interval: -1.2, 0.1), driven exlusively by an effect on plasma ammonia normalization.(1)

REFERENCES

Number	Reference
1	Carbaglu prescribing information. Recordati Rare Diseases Inc. August 2021.
2	Ah Mew N, Simpson KL, Gropman AL, et al. Urea Cycle Disorders Overview. April 2003 [Updated June 2017]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available at: http://www.ncbi.nlm.nih.gov/books/NBK1217/.
3	Rare Diseases Clinical Research Network. Urea Cycle Disorders Consortium. Urea Cycle Disorders Treatment Guidelines. Available at: https://www.rarediseasesnetwork.org/cms/ucdc/Healthcare-Professionals/Urea-Cycle-Treatment-Guidelines.
4	Summar M. Urea Cycle Disorders. National Organization for Rare Disorders (NORD). Available at: https://rarediseases.org/physician-guide/urea-cycle-disorders/.
5	Haberle J, Burlina A, Chakrapani A, et al. Suggested Guidelines for the Diagnosis and Management of Urea Cycle Disorders: First Revision. J Inherit Metab Dis. 2019;42(6):1041-1230.
6	Baumgartner MR, Horster F, Dionisi-Vici C, et al. Proposed Guidelines for the Diagnosis and Management of Methylmalonic and Propionic Acidemia. Orphanet J Rare Dis. 2014 Sep;9(130):1-36.
7	Manoli I, Sloan JL, Venditti CP. Isolated Methylmalonic Acidemia. 2005 Aug [Updated 2022 Sep]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available at: https://www.ncbi.nlm.nih.gov/books/NBK1231/.
8	Jurecki E, Ueda K, Frazier D, et al. Nutrition Management Guideline for Propionic Acidemia: An Evidence- and Consensus-Based Approach. Mol Genet Metab. 2019 Apr;126(4):341-354.

POLICY AGENT SUMMARY PRIOR AUTHORIZATION

Target Brand Agent(s)	Target Generic Agent(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
Carbaglu	carglumic acid soluble tab	200 MG	M ; N ; O ; Y	O ; Y		

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Carbaglu	carglumic acid soluble tab	200 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. ALL of the following: 1. The patient has a diagnosis of N-acetylglutamate synthase (NAGS) deficiency confirmed by enzyme analysis (via liver biopsy) OR genetic testing **AND** 2. The patient has a diagnosis of hyperammonemia AND ALL of the following: A. The patient has elevated ammonia levels according to the patient's age [Neonate: plasma ammonia level 150 µmol/L (> 260 µg/dl) or higher; Older child or adult: plasma ammonia level > 100 µmol/L (175 µg/dl)] **AND** B. The patient has a normal anion gap **AND** C. The patient has a normal blood glucose level **AND** 3. The patient is unable to maintain a plasma ammonia level within the normal range with the use of a protein restricted diet and, when clinically appropriate, essential amino acid supplementation **OR** B. ALL of the following: 1. ONE of the following: A. The patient has a diagnosis of methylmalonic acidemia (MMA) **OR** B. The patient has a diagnosis of propionic acidemia (PA, PROP) **AND** 2. The requested drug will be used as adjunctive therapy to standard of care for the treatment of acute hyperammonemia **AND** 3. The patient was hospitalized with a plasma ammonia level ≥70 µmol/L **AND** 2. ONE of the following: A. The requested agent is a generic equivalent **OR** B. The patient has tried and had an inadequate response to the generic equivalent **OR** C. The patient has an intolerance or hypersensitivity to the generic equivalent that is not expected to occur with the brand agent **OR** D. The patient has an FDA labeled contraindication to the generic equivalent that is not expected to occur with the brand agent **OR** E. The prescriber has provided information to support the use of the requested brand agent over the generic equivalent **OR** F. The patient is currently being treated with the requested agent as indicated by ALL of the following: 1. A statement by the prescriber that the patient is currently taking the requested agent **AND** 2. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on the requested agent **AND** 3. The prescriber states that a change in therapy is expected to be ineffective or cause harm **OR** G. The prescriber has provided documentation that the generic equivalent cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., nephrologist, metabolic disorders) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 5. The requested quantity (dose) is within FDA labeled dosing for the requested indication

Module	Clinical Criteria for Approval
	Length of Approval: Methylmalonic acidemia (MMA) or propionic acidemia (PA): 1 month NAGS deficiency: 12 months **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process (note Carbaglu for methylmalonic acidemia [MMA] or propionic acidemia [PA] should always be reviewed under Initial Evaluation) **AND** 2. The patient has had clinical benefit with the requested agent as evidenced by plasma ammonia level within the normal range **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., nephrologist, metabolic disorders) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 5. The requested quantity (dose) is within FDA labeled dosing for the requested indication **Length of Approval:** 12 months

