**Drug Use Research & Management Program**
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
**Phone** 503-947-5220 | **Fax** 503-947-2596

# **New Drug Evaluation:** Carbaglu® (carglumic acid) tablets for oral suspension

**Date of Review:** December 2025
**Generic Name:** carglumic acid

**End Date of Literature Search:** 09/10/2025
**Brand Name (Manufacturer):** CARBAGLU (Recordati Rare Diseases Group)
**Dossier Received**: No

**Plain Language Summary:**

- This review looks at evidence for carglumic acid, a medicine used to treat urea cycle disorders, which are conditions that are caused when a person cannot remove waste ammonia from their body.
- People with urea cycle disorders get sick when there is too much ammonia in the blood. Too much ammonia can lead to confusion, permanent brain damage, and death. Many people with urea cycle disorders become sick as newborns or very young babies.
- People with urea cycle disorders are treated by monitoring food (protein) intake and taking certain amino acids (protein is made of amino acids) supplements. CARBAGLU (carglumic acid) is used to manage a condition called N-acetyl glutamate synthetase (NAGS) deficiency, which is one kind of urea cycle disorder.
- Carglumic acid is also approved to treat a rare group of disorders called organic acidemias. In these conditions, the body does not have the enzymes needed to break down amino acids which results in a buildup of acids in the blood. Symptoms include poor feeding, vomiting, weak muscle tone, and lack of energy. Studies have shown that propionic acidemia and methylmalonic acidemia can be treated with carglumic acid.
- The Drug Use Research and Management group recommends that the Oregon Health Authority pay for carglumic acid in patients with NAGS deficiency or organic acidemias that are indicated by the Food and Drug Administration after their provider documents medical appropriateness through a process called prior authorization.

**Research Questions:**

1. What is the efficacy and effectiveness of carglumic acid in managing specific urea cycle disorders, including n-acetyl glutamate synthetase (NAGS) deficiency, propionic acidemia (PA), and methylmalonic acidemia (MMA)?
2. What are the harms of carglumic acid for the management of NAGS, PA, and MMA?
3. Are there subgroups of patients based on demographics (e.g., age, racial or ethnic groups, gender), other medications, or co-morbidities for which carglumic acid is more effective or associated with fewer adverse events?

**Conclusions:**

- Carglumic acid is FDA-approved as adjunctive therapy for the acute and chronic treatment of acute hyperammonemia due to NAGS deficiency and as adjunctive therapy to standard of care for the treatment of acute hyperammonemia due to PA or MMA.[1]

Author: Deanna Moretz, PharmD, BCPS

- The efficacy of carglumic acid in the treatment of acute and chronic hyperammonemia due to NAGS deficiency was evaluated in an unpublished, retrospective case series of 23 NAGS deficiency patients treated with carglumic acid over a median duration of 7.9 years (range 0.6 to 20.8 years).[1] Short-term efficacy was evaluated using mean and median change in plasma ammonia levels from baseline to days 1 to 3.[1] Persistence of the effect was evaluated using long-term mean and median change in plasma ammonia level.[1] By day 3 of treatment with carglumic acid mean plasma ammonia levels had normalized (43.3 micromol/L; 95% CI, 0.5 to 86.2) and remained within or near normal range during long-term treatment, which ranged from 7 to 249 months (51.9 micromol/L; 95% Confidence Interval [CI], 11.4 to 92.1; low-quality evidence).[1]
- A randomized, double-blind, placebo-controlled, multicenter clinical trial evaluated the efficacy of carglumic acid in the treatment of hyperammonemia in patients with PA and MMA (NCT01599286).[1] The study is not published, and study details are limited to the prescribing information issued by the manufacturer. Participants with an eligible hyperammonemic episode, defined as an admission to the hospital with a plasma ammonia level 70 micromol/L or higher, were randomized 1:1 to receive either carglumic acid or placebo for 7 days or until hospital discharge, whichever occurred first.[1] The primary endpoint was the time from the first dose of drug to the earlier of plasma ammonia level of 50 micromol/L or less (normal range) or hospital discharge.[1] The median time to reach the primary endpoint was 1.5 days in the carglumic acid group compared to 2.0 days in the placebo group, a difference of 0.5 days (95% CI, -1.2 to 0.1; not significant; low-quality evidence).[1] Throughout the first 3 days of treatment, a higher proportion of carglumic acid-treated episodes reached the primary endpoint compared to placebo-treated episodes.[1]
- In the retrospective case series of 23 NAGS deficiency patients treated with carglumic acid, 17 of the 23 patients reported an adverse reaction.[1] The most common adverse reactions (occurring in ≥ 13% of patients) were vomiting, abdominal pain, pyrexia, tonsillitis, anemia, diarrhea, ear infection, infections, nasopharyngitis, decreased hemoglobin, and headache.[1] **Table 1** summarizes adverse reactions that occurred in 2 more patients who received carglumic acid in the retrospective case series.
- In a randomized, double-blind, placebo-controlled clinical trial, 24 patients (15 with PA and 9 with MMA) at least 1 adverse reaction was reported during the course of hyperammonemic episodes in 42% of hyperammonemic episodes.[1] The most common adverse reactions (≥ 5%) during hyperammonemic episodes were neutropenia, anemia, vomiting, electrolyte imbalance, decreased appetite, hypoglycemia, lethargy/stupor, encephalopathy and pancreatitis/lipase increased.[1] **Table 2** summarizes adverse reactions reported during hyperammonemic episodes in patients with PA or MMA treated with carglumic acid or placebo.[1]
- There is insufficient evidence to determine if there are subgroups of patients based on demographics (e.g., age, racial or ethnic groups, gender), other medications, or co-morbidities for which carglumic acid is more effective or associated with fewer adverse events.

**Recommendations:**
- Make one carglumic acid product preferred on the Preferred Drug List with clinical prior authorization (PA) criteria to ensure use in appropriate populations (**Appendix 3**).
- After review of drug costs in executive session, make CARBAGLU dispersible tablets preferred and make generic carglumic acid non-preferred.

**Background:**
The urea cycle consists of a series of enzymes that function interdependently to convert ammonia, a product of protein catabolism, into urea, a molecule that can be excreted into the urine.[2] Urea cycle disorders result from a deficiency of any of the following enzymes: N-acetylglutamate synthase (NAGS), carbamyl phosphate synthetase 1 (CPS 1), ornithine transcarbamylase (OTC), argininosuccinate synthetase (AS), argininosuccinate lyase (AL), or arginase (ARG).[3] These disorders are autosomal recessive diseases with the exception of OTC deficiency, which is an X-linked disorder.[2] Urea cycle disorders have an overall prevalence

of approximately 1 in 30,000 live births.[2] Ornithine transcarbamylase deficiency is the most common urea cycle disorder, while NAGS deficiency is one of the rarest.[2]

Hyperammonemia is the primary pathophysiologic consequence of NAGS deficiency and other urea cycle disorders.[2] Hyperammonemia leads to multiple biochemical and structural changes in the brain, and is thought to cause swelling of astrocytes in the brain as well as pleomorphic changes in the mitochondria.[2] The brain lacks a complete urea cycle and relies on the synthesis of glutamine to remove excess ammonia and to store temporary nitrogen.[2] This process is primarily localized in the astrocytes, such that hyperammonemia leads to accumulation of glutamine from glutamate and ammonia via glutamine synthetase.[2] Excess glutamine is released into the extracellular space, altering astrocyte-neuronal transmission.[2] This creates an imbalance of excitatory versus inhibitory neurotransmission because of increased glutamate production combined with decreased synaptic uptake of glutamate.[2] It is thought that acute hyperammonemia leads to changes in astrocyte protein expression, glutamine synthetase, glial fibrillary acidic protein, glutamate transporter, nitric oxide synthase, and peripheral benzodiazepine receptors.[2] These changes alter the brain's ability to remove additional ammonia, to regulate cerebral blood flow, to maintain energy homeostasis and neurotransmission.[2]

NAGS deficiency is an extremely rare disease, with about 50 known cases reported worldwide.[4] N-acetyl glutamate synthase is an enzyme that is essential for the function of the urea cycle.[2] It is located in the liver and intestine.[2] Patients with NAGS deficiency are unable to synthesize urea from ammonia.[2] Inherited NAGS deficiency results from one or more mutations in the NAGS gene, which causes an absence or a decrease in the enzyme activity.[2] Without the co-factor NAG, CPS 1 is catalytically inactive.[2]

The autosomal recessive disorder expresses phenotypes that range from acute neonatal onset to late-onset disease in adults.[2] The neonatal-onset phenotype has a destructive clinical course, and usually reflects complete absence of NAGS activity.[2] Symptoms result primarily from hyperammonemia.[2] Newborns who have hyperammonemia may present with respiratory alkalosis, hypotonia, lethargy, and vomiting.[2] Symptoms may progress to include cerebral edema, seizures, and death. If newborns survive the acute hyperammonemic episode, they usually tend to exhibit significant development delays, residual neurologic impairments and seizure disorder.[2]

Late-onset NAGS deficiency has a variable age of onset, and the degree of residual enzyme activity is heterogeneous.[2] Patients with partial NAGS deficiency may present with their initial symptoms anywhere from the first year of life to adulthood.[2] In infants, they may become symptomatic following weaning from breast milk or a change from a lower protein infant formula to cow's milk.[2] In children and adults, events such as acute infection, a high dietary protein load, or a combination of the two may lead to hyperammonemia.[2] Symptoms result primarily from hyperammonemia, and the most common clinical findings include central nervous system symptoms such as lethargy, irritability, or somnolence.[2] These symptoms may progress to agitation, disorientation, combativeness, ataxia, and amblyopia.[2] Children with partial enzymatic defects tend to have better outcomes than the ones with complete absence of NAGS activity.[2] Children with partial NAGS deficiency may exhibit cognitive dysfunction such as learning disabilities and attention deficit hyperactivity disorders.[2]

Organic acidemias are a rare class of inborn errors of metabolism characterized by accumulation of organic acid metabolites and a poor prognosis.[5] Most organic acidemias become apparent during the newborn period or in early infancy.[5] Hyperammonemia in patients with MMA and PA is caused by accumulation of propionyl-CoA which decreases the synthesis of NAG the natural activator of CPS 1.[6] The overall incidences of PA and MMA in Western populations have been estimated at up to 1/150,000 and 1/50,000 births, respectively, although the incidences are much higher in some countries.[7] 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.[7] Mental outcome tends to be worse in PA. Late complications include chronic kidney disease almost

exclusively in MMA and cardiomyopathy mainly in PA.[7] The treatment of these conditions is focused on managing acute hyperammonemia.[5] First-line medications, range from nitrogen scavengers, carglumic acid, and carnitine to continuous hemodiafiltration.[5] Long-term management focuses mainly on a protein-restricted diet while monitoring the patients' daily needs for normal growth and development and administration of l-carnitine and metronidazole.[8]

Beginning in January 2026, the Oregon Health Authority is proposing that high cost medications for rare conditions be carved out of Coordinated Care Organization (CCO) payments and billed directly to fee-for-service (FFS). Medications can be included in this carve-out if they meet the following criteria:

1. Estimated acquisition cost of more than $500,000 per member over a 12-month period
2. Are indicated for rare conditions, and
3. Have few alternatives, as determined by the Oregon Health Authority

In the past year (September 2024 to September 2025), 11 patients enrolled in OHP CCOs and 2 patients in the FFS population had claims for the NAGS diagnosis. There are 2 patients in the CCO population with a diagnosis of PA, while 31 CCO patients have a diagnosis of MMA. For the FFS population, no patients had claims for a diagnosis of PA, while 4 patients had claims for MMA.

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations. Pharmacology and Pharmacokinetic Properties are listed in **Appendix 2**.

**Clinical Efficacy:**

Carglumic acid is FDA-approved in pediatric and adult patients as: 1) adjunctive therapy to standard of care for the treatment of acute hyperammonemia due to NAGS deficiency; 2) maintenance therapy for the treatment of hyperammonemia due to NAGS deficiency; and 3) adjunctive therapy to standard of care for the treatment of acute hyperammonemia due to PA or MMA.[1]

The efficacy of carglumic acid in the treatment of acute and chronic hyperammonemia due to NAGS deficiency was evaluated in an unpublished, unblinded, uncontrolled, retrospective case series of 23 NAGS deficiency patients treated with carglumic acid over a median duration of 7.9 years (range 0.6 to 20.8 years).[1] For acute treatment, patients received carglumic acid at 100 mg/kg/day to 250 mg/kg/day orally administered in 2 to 4 divided doses.[1] For maintenance treatment, the dosage was reduced over time based on plasma ammonia level and clinical response.[1] Fourteen males (61%) and 9 females (39%) received carglumic acid in the case series.[1] The mean age at initiation of carglumic acid therapy was 2 years (range 0 to 13 years).[1] The 23 patients were treated with carglumic acid at 14 sites that were either hospitals or outpatient clinics located in the Netherlands, Germany, France, United Kingdom, Sweden, Italy, Spain, and Austria.[2] Most patients were treated in France.[2]

The clinical and biochemical data in the case series could not be formally analyzed using statistical testing.[1] Short-term efficacy was evaluated using mean and median change in plasma ammonia levels from baseline to days 1 to 3.[1] Persistence of the effect was evaluated using long-term mean and median change in plasma ammonia level.[1] Of the 23 patients with NAGS deficiency in the case series, 13 patients had documented plasma ammonia levels prior to, and after long-term treatment with, carglumic acid.[1] All 13 patients had increased plasma ammonia levels at baseline (mean 271 micromol/L; normal range: 5 to 50 micromol/L).[1] By day 3 of treatment with carglumic acid, mean plasma ammonia levels had normalized (43.3 micromol/L; 95% CI, 0.5 to 86.2) and remained within or near normal range during long-term treatment, which ranged from 7 to 249 months (51.9 micromol/L; 95% CI, 11.4 to 92.1; low-quality evidence).[1]

A randomized, double-blind, placebo-controlled, multicenter clinical trial evaluated the efficacy of carglumic acid in the treatment of hyperammonemia in 24 patients with PA or MMA (NCT01599286).[1] This study is not published, and study details are limited to the prescribing information issued by the manufacturer. Eligible hyperammonemic episodes, defined as an admission to the hospital with a plasma ammonia level 70 micromol/L or greater, were randomized 1:1 to receive either carglumic acid or placebo for 7 days or until hospital discharge, whichever occurred earlier.[1] All patients received standard of care, including a combination of protein restriction, intravenous glucose, insulin, and/or L-carnitine; the use of alternative pathway medications (e.g., sodium benzoate and medications with phenylacetate as an active metabolite) was prohibited.[1] Carglumic acid was dosed orally at 150 mg/kg/day for patients who weighed 15 kg or less, or 3.3 g/$m^2$ /day for patients who weighed more than 15 kg. The daily dose was divided into 2 equal doses administered 12 hours apart by NG tube, G-tube, or oral syringe.[1] Plasma ammonia testing was performed at pre-randomization and at post-dosing intervals of every 6-12 hours for the first 48 hours and every day thereafter if the ammonia level was 50 micromol/L or higher.[1]

The efficacy evaluation was based on 90 hyperammonemic episodes (42 treated with carglumic acid and 48 with placebo) in 24 patients (12 male and 12 female) with PA (n = 15) or MMA (n = 9).[1] The median patient age was 8 years (range 4 days to 29 years).[1] The primary endpoint was the time from the first dose of drug to the earlier of plasma ammonia level of 50 micromol/L or less (normal range) or hospital discharge.[1] The median time to reach the primary endpoint was 1.5 days in the carglumic acid group compared to 2.0 days in the placebo group, a difference of 0.5 days (95% CI, -1.2 to 0.1; not significant; low-quality evidence).[1] In the first 3 days, a higher proportion of carglumic acid-treated episodes reached the primary endpoint compared to placebo-treated episodes.[1]

An additional, prospective, randomized, open-label study funded by the manufacturer compared the efficacy of adding carglumic acid (50 mg/kg/day in divided doses, twice daily) to standard treatment in patients with PA and MMA.[5] Standard treatment followed the most recent guidelines of l-carnitine (150 mg/kg/day divided and given every 8 h), metronidazole (15 mg/kg/day divided and given every 8 h for one week each month), and a protein-restricted diet.[8] The study was conducted in 2 tertiary care centers in Saudi Arabia. The study was open-label as patients might present to the ER with acute crises, where the attending physicians would need the details of their treatment regimens.[5] Additionally, according to the emergency protocol for the management of PA and MMA, carglumic acid is considered a rescue medication and should be used in all patients with hyperammonemia, even for those in the standard treatment arm.[5] The primary outcome was long-term effectiveness (2 years) of carglumic acid in reducing the number of emergency department (ED) admissions due to hyperammonemia in patients with PA or MMA.[5] Secondary outcomes included comparing effects on plasma ammonia levels from baseline to the end of the study, time to the first episode of hyperammonemia, levels of relevant biochemical biomarkers including plasma amino acids, acylcarnitine profile, and urine organic acids.[5]

Thirty-eight patients were enrolled in the study, 21 were randomized to carglumic acid plus standard therapy and 17 were allocated to the standard therapy arm.[5] The study included patients aged ≤ 15 years whose parents or legal guardians had provided written consent and were not participating in any other trial.[5] PA was confirmed by measuring acylcarnitine profile, urine organic acid, propionyl-CoA carboxylase in leukocytes or cultured fibroblasts, or by DNA molecular testing of the PCCA or PCCB genes.[5] MMA was confirmed by measuring acylcarnitine profile, urine organic acid, methyl malonyl-CoA mutase in cultured fibroblasts, or DNA molecular testing of the MUT gene.[5] Only patients with an expected survival of ≥ 6 months were included in the study.[5] These were defined as those not admitted to the pediatric intensive care unit (PICU) for > 2 times/year because of hyperammonemia, asymptomatic patients diagnosed by newborn screening, or stable chronic patients who were followed up at the outpatient clinic.[5] Genotyping was performed on all participants to confirm the diagnosis.[5]

The patients included 27 boys and 11 girls, almost equally distributed between the two arms.[5] Of the 21 patients allocated to receive carglumic acid, 5 did not return after the screening visit and were excluded from the analysis.[5] During the trial, two patients in the carglumic acid arm underwent liver transplantation and discontinued the follow-up visits; however, their data were included in the final analysis.[5] Although one patient from the standard treatment arm was lost to

follow-up after four visits, their data were included in the final analysis.[5] Sixteen patients were analyzed in the carglumic acid plus standard therapy cohort and 17 patients were analyzed in the standard therapy only cohort.[5] The mean age of the participants in the standard treatment arm was approximately 36 months, while the mean age in the carglumic acid arm was approximately 40 months.[5] All other demographic characteristics between the two arms were evenly distributed.[5]

The total number of ED admissions was 12.76 in the standard treatment group and 6.31 in the carglumic acid group over 24 months.[5] Results of the Poisson regression analysis suggest that carglumic acid achieved a 51% significant reduction in the number of ED admissions compared to standard therapy (rate ratio, 0.4945; 95% CI, 0.2904 to 0.8422; p = 0.0095).[5] The plasma ammonia levels from the baseline and at the end of the study did not show any significant difference between the arms.[5] When the times of the first episode of hyperammonemia were compared using the Kaplan–Meier curve, both arms had a comparable course.[5] For the biochemical markers, there was a significant difference in the level of plasma glycine favoring the carglumic acid arm (p = 0.046).[5] There were no significant differences in the levels of other plasma amino acids.[5]

**Clinical Safety:**

In a retrospective case series of 23 NAGS deficiency patients treated with carglumic acid, 17 of the 23 patients reported an adverse reaction.[1] The most common adverse reactions (occurring in ≥ 13% of patients) were vomiting, abdominal pain, pyrexia, tonsillitis, anemia, diarrhea, ear infection, infections, nasopharyngitis, decreased hemoglobin, and headache.[1] **Table 1** summarizes adverse reactions that occurred in 2 more patients who received carglumic acid in the retrospective case series.

**Table 1. Adverse Reactions Reported In Patients With NAGS Deficiency Treated With Carglumic Acid In A Retrospective Case Series[1]**

| Adverse Reaction | Number of Patients (%) |
|---|---|
| Vomiting | 6 (26) |
| Abdominal Pain | 4 (17) |
| Pyrexia | 4 (17) |
| Tonsillitis | 4 (17) |
| Anemia | 3 (13) |
| Diarrhea | 3 (13) |
| Ear Infection | 3 (13) |
| Infections | 3 (13) |
| Nasopharyngitis | 3(13 |
| Decreased Hemoglobin | 3 (13) |
| Headache | 3 (13) |
| Dysgeusia | 2(9) |
| Asthenia | 2 (9) |
| Hyperhidrosis | 2 (9) |
| Influenza | 2 (9) |
| Pneumonia | 2 (9) |
| Decreased Weight | 2 (9) |
| Anorexia | 2 (9) |

| | |
|---|---|
| Somnolence | 2 (9) |
| Rash | 2 (9) |
| Abbreviations: NAGS = N-acetylglutamate synthetase | |

In a randomized, double-blind, placebo-controlled clinical trial, 24 patients (15 with PA and 9 with MMA) at least 1 adverse reaction was reported during the course of hyperammonemic episodes in 42% of hyperammonemic episodes.[1] The most common adverse reactions (≥5%) during hyperammonemic episodes were neutropenia, anemia, vomiting, electrolyte imbalance, decreased appetite, hypoglycemia, lethargy/stupor, encephalopathy and pancreatitis/lipase increased.[1] **Table 2** summarizes adverse reactions reported during hyperammonemic episodes in patients with PA or MMA treated with carglumic acid or placebo.[1]

**Table 2: Adverse Reactions During Hyperammonemic Episodes in Patients with PA or MMA Treated with Carglumic Acid or Placebo[1]**

| **Adverse Reaction** | **Carglumic Acid (n = 42 episodes) N (%)** | **Placebo (n = 48 episodes) N (%)** |
|---|---|---|
| Neutropenia | 6 (14) | 4 (8) |
| Anemia | 5 (12) | 4 (8) |
| Vomiting | 3 (7) | 1 (2) |
| Electrolyte Imbalance | 3 (7) | 1 (2) |
| Decreased Appetite | 2 (5) | 1 (2) |
| Hypoglycemia | 2 (5) | 1 (2) |
| Lethargy/Stupor | 2 (5) | 1 (2) |
| Encephalopathy | 2 (5) | 0 |
| Pancreatitis/Increased Lipase | 2 (5) | 0 |
| Cardiomyopathy | 1 (2) | 0 |
| Increased Alanine Aminotransferase | 1 (2) | 0 |
| Increased Aspartate Aminotransferase | 1 (2) | 0 |
| Infusion Site Extravasation | 1 (2) | 0 |
| Increased White Blood Cell Count | 1 (2) | 0 |
| Behavior Disorder | 1(2) | 0 |
| Sleep Disorder | 1 (2) | 0 |
| Apnea | 1 (2) | 0 |
| Hyperventilation | 1 (2) | 0 |
| Abbreviations: MMA = methylmalonic acidemia; PA = propionic acidemia | | |

No dosage adjustment is warranted in patients with mild renal impairment (eGFR 60-89 mL/min/1.73 $m^2$).[1] The dose of carglumic acid in patients with moderate or severe renal impairment must be modified according to the specific indication as outlined by the manufacturer in the prescribing information.

**References:**


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**Appendix 1:** Prescribing Information Highlights

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

**These highlights do not include all the information needed to use CARBAGLU safely and effectively. See full prescribing information for CARBAGLU.**

**CARBAGLU® (carglumic acid) tablets for oral suspension**
**Initial U.S. Approval: 2010**

**----------INDICATIONS AND USAGE----------**

CARBAGLU is a carbamoyl phosphate synthetase 1 (CPS 1) activator indicated in pediatric and adult patients as:

- Adjunctive therapy to standard of care for the treatment of acute hyperammonemia due to N-acetylglutamate synthase (NAGS) deficiency. (1.1)
- Maintenance therapy for the treatment of chronic hyperammonemia due to NAGS deficiency. (1.1)
- Adjunctive therapy to standard of care for the treatment of acute hyperammonemia due to propionic acidemia (PA) or methylmalonic acidemia (MMA). (1.2)

**----------DOSAGE AND ADMINISTRATION----------**

Acute Hyperammonemia due to NAGS deficiency (2.2)

- The recommended dosage in adult and pediatric patients is 100 mg/kg to 250 mg/kg orally daily. Divide the daily dosage into 2 to 4 doses.

Chronic Hyperammonemia due to NAGS deficiency (2.2)

- The recommended dosage in adult and pediatric patients is 10 mg/kg to 100 mg/kg orally daily. Divide the daily dosage into 2 to 4 doses.

Therapeutic Monitoring for NAGS Deficiency (2.2)

- Closely monitor plasma ammonia and titrate dosage to maintain the ammonia level within normal range for the patient's age, taking into consideration their clinical condition.

Acute Hyperammonemia due to PA or MMA (2.3)

- The recommended dosage in adult and pediatric patients is:
  - 150 mg/kg orally daily for patients less than or equal to 15 kg
  - 3.3 g/m$^2$ orally daily for patients greater than 15 kg
- Divide the daily dosage into 2 doses.
- Continue treatment until ammonia level is less than 50 micromol/L and for a maximum duration of 7 days.

Patients with Renal Impairment (2.4)

- See Full Prescribing Information for Instructions on Dosage Adjustment.

Preparation and Administration (2.5)

- Disperse CARBAGLU tablets in water. Do not swallow whole or crushed.
- Take immediately before meals or feedings.
- For additional instructions on preparation and administration orally or through a nasogastric tube or gastrostomy tube, see Full Prescribing Information.

**----------DOSAGE FORMS AND STRENGTHS----------**

Tablets for oral suspension: 200 mg, functionally scored. (3)

**----------CONTRAINDICATIONS----------**

None. (4)

**----------ADVERSE REACTIONS----------**

- NAGS deficiency: Most common adverse reactions (≥13%) are vomiting, abdominal pain, pyrexia, tonsillitis, anemia, diarrhea, ear infection, infections, nasopharyngitis, hemoglobin decreased, and headache. (6.1)
- PA and MMA: Most common adverse reactions (≥5%) are neutropenia, anemia, vomiting, electrolyte imbalance, decreased appetite, hypoglycemia, lethargy/stupor, encephalopathy and pancreatitis/lipase increased. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Recordati Rare Diseases Inc. at 1-888-575-8344, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**

**Revised: 1/2024**

**Appendix 2.** Pharmacology and Pharmacokinetic Properties.[1]

| **Parameter** | |
|---|---|
| Mechanism of Action | Carbamoyl phosphate synthetase 1 (CPS 1) activator |
| Oral Bioavailability | 10% |
| Distribution and Protein Binding | Volume of distribution: 15 \L/kg (after IV infusion). Not bound to plasma proteins. |
| Elimination | 9% of products is excreted by the kidneys as unchanged product and 60% is recovered unchanged in the feces. |
| Half-Life | 25 hours |
| Metabolism | A proportion of carglumic acid may be metabolized by intestinal bacterial flora. Likely end product of metabolism is carbon dioxide, eliminated through the lungs. |

Abbreviations: kg = kilograms; L = Liters

# Carglumic Acid

**Goal(s):**
- Ensure appropriate utilization of carglumic acid in FDA-approved indications
- Incorporate 2-step review process for drugs on the high-cost drug carve-out list.

**Length of Authorization:** Up to 12 months

**Requires PA:**
- CARBAGLU (carglumic acid) tablets for oral suspension for FFS and CCO patients

**Covered Populations:** FFS and CCO enrolled patients starting 1/1/26

**Covered Alternatives:**
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

| Approval Criteria | | |
|---|---|---|
| 1. What diagnosis is being treated? | Record ICD10 code. | |
| 2. Is this a request for continuation of therapy? | **Yes:** Go to Renewal Criteria | **No:** Go to #3 |
| 3. Is this an FDA approved indication? | **Yes:** Go to #4 | **No:** Pass to RPh. Deny; medical appropriateness |
| 4. Is the request for therapy to treat hyperammonemia due to N-acetyl glutamate synthetase (NAGS) deficiency treatment of acute hyperammonemia due to propionic acidemia (PA) or methylmalonic acidemia (MMA)? | **Yes**: Go to #5 | **No:** Pass to RPh. Deny; medical appropriateness |
| 5. Has the diagnosis been confirmed by genetic testing? | **Yes:** Go to #6 | **No:** Pass to RPh. Deny; medical appropriateness |

| Approval Criteria | | |
|---|---|---|
| 6. Is the patient on a protein restricted diet? | **Yes:** Go to #7 | **No:** Pass to RPh. Deny; medical appropriateness |
| 7. Have baseline ammonia levels been documented? | **Yes:** Go to #8<br><br>Document date and results<br><br>_____ | **No:** Pass to RPh. Deny; medical appropriateness |
| 8. Is the medication prescribed by or in consultation with a provider with expertise in managing urea cycle disorders or organic acidemias? | **Yes:** Go to #9 | **No:** Pass to RPh. Deny; medical appropriateness |
| 9. Is the request for a preferred product? | **Yes:** Pass to RPh. Pend; Refer to DMAP for secondary review.<br><br>Duration: Approvals cover up to 12 months. | **No:** Pass to RPh. Deny; medical appropriateness |

| Renewal Criteria | | |
|---|---|---|
| 1. Is the request to renew therapy for treatment of hyperammonemia due to NAGS deficiency, or treatment of acute hyperammonemia due to PA or MMA? | **Yes**: Go to #2 | **No:** Pass to RPh. Deny; medical appropriateness |
| 2. Has the patient's condition improved as assessed by the prescribing provider and the provider attests to patient's improvement? | **Yes:** Pass to RPh. Pend; Refer to DMAP for secondary review.<br><br>Duration: Approvals cover up to 12 months. | **No:** Pass to RPh. Deny; medical appropriateness |