Hyperammonemia due to NAGS deficiency may occur at any time of life

**INDICATIONS AND USAGE**

CARBAGLU® (carglumic acid) is a Carbamoyl Phosphate Synthetase 1 (CPS1) activator 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, is recommended.

- **Maintenance therapy** in pediatric and adult patients for the treatment of chronic hyperammonemia due to the deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS). During maintenance therapy, the concomitant use of other ammonia lowering therapies and protein restriction may be needed based on plasma ammonia levels.

**IMPORTANT SAFETY INFORMATION**

- Most common adverse reactions (>9%) are: vomiting, abdominal pain, pyrexia, tonsillitis, anemia, diarrhea, ear infection, infections, nasopharyngitis, hemoglobin decreased, and headache.
UREA CYCLE AND DEFECTS

- In humans, nitrogen is produced by catabolism of proteins and other nitrogen-containing molecules
- The urea cycle converts waste nitrogen into urea
- Deficiency of enzymes in the urea cycle may lead to a build-up of ammonia, which is neurotoxic

Interruption of the urea cycle causes hyperammonemia which, if untreated, may result in coma and death

The mortality rate during hyperammonemic crises can reach 10%

IMPORTANT SAFETY INFORMATION

- Hyperammonemia: Monitor plasma ammonia level during treatment. Prolonged exposure to elevated plasma ammonia level can result in brain injury or death. Prompt use of all therapies necessary to reduce plasma ammonia level is essential.
- Pregnancy: No human data; decreased survival and growth in animal offspring.
- Nursing Mothers: Breastfeeding is not recommended while taking CARBAGLU.
DIAGNOSTIC ALGORITHM FOR HYPERAMMONEMIA IN UCDs

HYPERAMMONEMIA

Glutamine Low/Normal

Glutamine Elevated

Organic Acidemias

Citrulline Low

Citrulline High

Urinary Orotic Acid Normal

Urinary Orotic Acid Elevated

NAGS deficiency

OTC deficiency

CPS1 deficiency

OAT deficiency

ARG1 deficiency

HHH syndrome

ASL deficiency

ASS deficiency

LP intolerance

NAGS: N-acetylglutamate synthase
CPS1: carbamoyl phosphate synthetase 1
OTC: ornithine transcarbamylase
OAT: ornithine aminotransferase
ARG1: arginase
HHH: hyperornithinemia-hyperammonemia-homocitrullinuria
ASL: argininosuccinate lyase
ASS: argininosuccinate synthase
LP: lysinuric protein


Genetic testing is virtually the only method that can confirm a diagnosis of NAGS deficiency. For more information consult the National Center for Biotechnology Information (NCBI) Genetic Testing Registry at www.ncbi.nlm.nih.gov/gtr

IMPORTANT SAFETY INFORMATION

- Hyperammonemia: Monitor plasma ammonia level during treatment. Prolonged exposure to elevated plasma ammonia level can result in brain injury or death. Prompt use of all therapies necessary to reduce plasma ammonia level is essential.
NAGS DEFICIENCY

- NAGS deficiency is a rare autosomal recessive urea cycle disorder
- The classic presentation of urea cycle disorders including primary NAGS deficiency is high levels of ammonia in the neonatal period

- Partial/milder enzyme deficiency may permit an individual to function normally until a stressor triggers a hyperammonemic crisis:
  - Valproic acid | Heart-lung transplant | Parenteral nutrition with high nitrogen intake
  - Post-partum stress | Short bowel and kidney disease | Gastrointestinal bleeding

NAGS DEFICIENCY IN LATE-ONSET PATIENTS: CLINICAL PRESENTATION

<table>
<thead>
<tr>
<th>GASTROINTESTINAL PRESENTATIONS</th>
<th>NEUROLOGICAL PRESENTATIONS</th>
<th>PSYCHIATRIC PRESENTATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Nausea, vomiting</td>
<td>- Disorientation</td>
<td>- Aggressive attitude</td>
</tr>
<tr>
<td></td>
<td>- Dilated pupils with delayed response to light</td>
<td>- Restlessness</td>
</tr>
<tr>
<td></td>
<td>- Exaggerated deep tendon reflexes</td>
<td>- Episodic altered mental status</td>
</tr>
<tr>
<td></td>
<td>- Generalized cerebral edema</td>
<td>- Confusion</td>
</tr>
<tr>
<td></td>
<td>- Unresponsiveness to stimuli</td>
<td>- Post-operative combativeness, combative behavior</td>
</tr>
<tr>
<td></td>
<td>- Seizures</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Atactic gait</td>
<td></td>
</tr>
</tbody>
</table>

BLOOD AMMONIA 113-4781 µmol/L*

* Normal blood ammonia level in adults: 11-32 µmol/L

DIAGNOSTIC CLUES AND MANAGEMENT

- Plasma ammonia should be measured promptly in all patients with unexplained encephalopathy, including cyclical manifestations, to identify possible underlying metabolic disorders
- Prompt diagnosis and initiation of treatment are necessary to avoid potentially poor neurological outcomes
- Patients should be managed by physicians and medical teams experienced in metabolic disorders
- The mainstay of ongoing management of NAGS deficiency is maintenance of plasma ammonia level in a normal range by avoiding catabolic stress and using carglumic acid

* Carglumic acid is the treatment of choice in NAGS deficiency *

IMPORTANT SAFETY INFORMATION

- Most common adverse reactions (>9%) are: vomiting, abdominal pain, pyrexia, tonsillitis, anemia, diarrhea, ear infection, infections, nasopharyngitis, hemoglobin decreased, and headache.
- 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.
ILLUSTRATIVE CASE OF NAGS DEFICIENCY DIAGNOSED IN A 38-YEAR-OLD MALE

20-year history of fluctuating behavioral changes associated with nausea and vomiting

### Past medical history

| Symptomatic (behavioral changes, confusion) in early childhood and adulthood | Ammonia levels never checked before hospitalization | Negative family history |

### Clinical course... in the emergency room

| Ongoing nausea, vomiting, headache | Stable vital signs | Behavioral disinhibition and fluctuating drowsiness |
| Impaired coordination | Normal cranial nerve examination and power testing | Significant asterixis (flapping tremor) |
| Mild spasticity on muscle tone assessment | | Otherwise unremarkable general examination |

### ... during hospital admission and follow-up

| High blood ammonia levels 434 µmol/L | Mild respiratory alkalosis | Normal head/spine MRI |
| Continuous EEG monitoring: generalized encephalopathy | Elevated glutamine level (1062 µmol/L), normal citrulline and urine amino acid levels | |

### Diagnosis

Molecular sequencing of the NAGS gene: compound heterozygote for E433G and IVS6+5 G>A, (both mutations) with residual NAGS expression that may explain the absence of neonatal hyperammonemia and delayed presentation in adult life

### Medical management

| Low protein diet | Initially sodium phenylbutyrate (200 mg TID*) and citrulline (50 mg/kg TID) |
| Switched to carglumic acid (1200 mg TID) with a more liberalized protein intake |

### Outcome

| Ammonia level returned to normal (29-35 µmol/L) | No hyperammonemic crisis for 2 years |
| Markedly improved behavior; short term memory loss remains |

* TID: three times a day
ORDERING CARBAGLU® (carglumic acid)

Exclusive Distribution Through Accredo

Representatives at Accredo Health Group, Inc. are committed to helping you and your patients through the ordering process. CARBAGLU is not available in retail pharmacies.

Patient Home Delivery
1. Download the CARBAGLU Prescription & Enrollment Form from the Accredo website (www.accredo.com).
2. Complete the CARBAGLU Prescription & Enrollment Form and fax it to the Accredo specialty pharmacy department at 1-888-454-8488.
3. A CARBAGLU specialty pharmacy representative may call to verify information and determine next steps. In some cases, prior authorization may be necessary.
4. Questions? Contact a CARBAGLU specialty pharmacy representative at 1-888-454-8860.

Hospital Orders – Emergency or Inpatient
1. Alert your hospital pharmacy that your patient requires CARBAGLU. Send an order for CARBAGLU to your hospital pharmacy and specify whether it is a STAT order (required in 6 hours or less*).
2. Ask your hospital pharmacy to call the wholesale department at Accredo at 1-877-900-9223 to place the order.
3. The wholesale department at Accredo will work with your hospital pharmacy to obtain payment information, establish shipping timelines, and verify the delivery address.
4. The Accredo specialty pharmacy team will follow up in 1-2 days to help set up patient home delivery of CARBAGLU, if applicable.

*Delivery time frame is weather dependent and is not guaranteed.

FINANCIAL ASSISTANCE PROGRAMS
For patients experiencing financial hardship, Recordati Rare Diseases Inc. supports a Patient Assistance Program and a Co-Pay Assistance Program, administered by Accredo. For more information, call: 1-888-454-8860.

For more information about CARBAGLU, visit: www.carbaglu.net

Please see enclosed Full Prescribing Information, including Instructions for Use.
CARBAGLU®
(carglumic acid) tablet for oral suspension

Initial U.S. Approval: 2010

1 INDICATIONS AND USAGE
1.1 Acute Hyperammonemia in Patients with NAGS Deficiency
CARBAGLU is indicated as an 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). (1.1)

1.2 Chronic Hyperammonemia in Patients with NAGS Deficiency
CARBAGLU is indicated as maintenance therapy in pediatric and adult patients for chronic hyperammonemia due to the deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS). (1.2)

DOSAGE AND ADMINISTRATION

Dosing (2.1):
• Acute Hyperammonemia: The recommended initial pediatric and adult dosage is 100 mg/kg/day to 250 mg/kg/day. Titrate based on plasma ammonia level and clinical symptoms.
• Maintenance for chronic hyperammonemia: The recommended pediatric and adult maintenance dosage is 10 mg/kg/day to 100 mg/kg/day. Titrate to target normal plasma ammonia level for age.
• Divide the total daily dose into two to four doses.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage
I. Acute Hyperammonemia in Patients with NAGS Deficiency
• For instructions on administration orally or through a nasogastric tube, see the full prescribing information.

Preparation and Administration (2.2):
• Disperse CARBAGLU tablets in water. Do not swallow whole or crushed.
• Take immediately before meals or feedings.
• For instructions on administration orally or through a nasogastric tube, see the full prescribing information.

ADVERSE REACTIONS

Most common adverse reactions (>9%) are: vomiting, abdominal pain, pyrexia, tinnitus, anemia, diarrhea, ear infection, infections, nasopharyngitis, hemorrhoglobin decreased, and headache. (6.1).

CONTRAINDICATIONS
None. (4)

WARNINGS AND PRECAUTIONS
Hyperammonemia: Monitor plasma ammonia level during treatment. Prolonged exposure to elevated plasma ammonia level can result in brain injury or death. Prompt use of all therapies necessary to decrease plasma ammonia level is essential. (5.1)

OVERDOSAGE

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.

USE IN SPECIFIC POPULATIONS

• Pregnancy: No human data; decreased survival and growth in animal offspring. (8.1)
• Nursing Mothers: Breastfeeding is not recommended while taking CARBAGLU. (8.3)
• See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling. Revised: 11/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

7 DESCRIPTION

10 OVERDOSAGE

11 CLINICAL PHARMACOLOGY

12 CLINICAL PHARMACOLOGY

13 NONCLINICAL TOXICOLOGY

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.
• Flush immediately with 1 to 2 mL of additional water to clear the NG tube.
• Flush the NG tube again, as needed, until no pieces of the tablet are left in the syringe or NG tube.

Preparation for Oral Administration Using an Oral Syringe in Pediatenic Patients
For administration via oral syringe, CARBAGLU should be administered as follows:
• Add about 2.5 mL of water into a small cup for each CARBAGLU tablet or each ½ CARBAGLU tablet needed for the prescribed dose.
• Add the CARBAGLU tablets to the water in the cup.
• Carefully stir the tablet and water mixture.
• Draw up the mixture in an oral syringe and administer immediately. Pieces of the tablet may remain in the oral syringe.
• Refill the oral syringe with a minimum volume of water (1 to 2 mL) and administer immediately.
• Flush the oral syringe again, as needed, until no pieces of the tablet are left in the syringe.

3 DOSAGE FORMS AND STRENGTHS
CARBAGLU is a white and elongated 200 mg tablet for oral suspension, functionally scored and coded “C” on one side.

5 WARNINGS AND PRECAUTIONS
5.1 Hyperammonemia
Any episode of acute symptomatic hyperammonemia should be treated as a life-threatening emergency. Treatment of severe hyperammonemia may require dialysis, preferably hemodialysis and/or hemofiltration, to reduce plasma ammonia concentration. Untreated hyperammonemia can result in brain damage and death, and prompt use of all therapies necessary to reduce plasma ammonia level is essential.

Since hyperammonemia in NAGS deficiency is the result of imbalance between ammonia detoxification capacity and protein catabolism, complete protein restriction during an acute hyperammonemic episode is recommended for no longer than 12 to 36 hours while maximizing caloric supplementation to reverse catabolism. Protein should be reintroduced as early as possible, following improvement of metabolic and clinical abnormalities in this setting. During long-term management, dietary protein restriction should be instituted to maintain blood ammonia level within an acceptable range for age. Ongoing monitoring of plasma ammonia level, neurological status, growth parameters, protein intake/nutritional status (both during acute hyperammonemic episodes and long-term), and relevant laboratory tests in patients receiving CARBAGLU should be part of evaluating the clinical response to treatment.

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.2 Pharmacodynamics
Carglumic acid acts as a CPS1 activator in patients with NAGS deficiency, thereby removing the block in the conversion of ammonia into urea, which is then excreted through the urine. Carglumic acid reduces plasma ammonia levels within 24 hours when administered with stearyl fumarate.

6.3 Pharmacokinetics
Carglumic acid is a synthetic structural analogue of N-acetylglutamate (NAG) which is produced from glutamate and acetyl-CoA in a reaction catalyzed by N-acetylglutamate synthase (NAGS), a mitochondrial liver enzyme. NAG acts as an essential allosteric activator of Carbamoyl Phosphate Synthetase 1 (CPS 1), a mitochondrial liver enzyme which catalyzes the first reaction of the urea cycle. The urea cycle, whose role is the disposition of ammonia, includes a series of biochemical reactions in the liver resulting in the conversion of ammonia into urea, which is then excreted through the urine. Carglumic acid acts as a CPS1 activator in patients with NAGS deficiency, thereby removing the block in the urea cycle and facilitating ammonia detoxification and urea production.

6.4 Pediatric Use
The efficacy of CARBAGLU for the treatment of hyperammonemia in patients with NAGS deficiency from birth to adulthood was evaluated in a retrospective review of the clinical course of 23 NAGS deficiency patients who all began CARBAGLU treatment during infancy or early childhood. There are no apparent differences in clinical response between adults and pediatric NAGS deficiency patients treated with CARBAGLU. However, data are limited.

6.5 Geriatric Use
CARBAGLU has not been studied in the geriatric population. Therefore, the safety and effectiveness in geriatric patients have not been established.

10 OVERDOSAGE
One patient treated with 650 mg/kg/day of carglumic acid developed symptoms characterized as a monosodium glutamate intoxication-like syndrome: tachycardia, profuse sweating, increased bronchial secretion, increased body temperature and restlessness. These symptoms resolved upon reduction of dose.

11 DESCRIPTION
CARBAGLU tablets for oral suspension, contain 200 mg of carglumic acid. Carglumic acid, the active substance, is a Carbamoyl Phosphate Synthetase 1 (CPS 1) activator and is soluble in boiling water, slightly soluble in cold water, and practically insoluble in organic solvents.

Chemically carglumic acid is N-carbamoyl-L-glutamic acid or (2S)-2-carbamoylamino)pentanedic acid, with a molecular weight of 190.16.

The structural formula is:

Molecular Formula: C_{16}H_{24}N_{2}O_{7}

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category C
There are no adequate and well controlled studies or available human data with CARBAGLU in pregnant women. Decreased survival and growth occurred in offspring born to animals that received carglumic acid at a dose approximately 38 times the maximum reported human maintenance dose. Because untreated N-acetylglutamate synthase (NAGS) deficiency results in irreversible neurologic damage and death, women with NAGS must remain on treatment throughout pregnancy.

No effects on embryofetal development were observed in pregnant rats treated with up to 2000 mg/kg/day (approximately 38 times the maximum reported human maintenance dose [100 mg/kg/day] based on AUC [area under the plasma concentration-time curve]) from two weeks prior to mating through organogenesis or in pregnant rabbits treated with up to 1000 mg/kg/day (approximately 6 times the maximum reported human maintenance dose [100 mg/kg/day] based on AUC). In a peri- and post-natal developmental study, female rats received oral carglumic acid from organogenesis through lactation at doses of 500 and 2000 mg/kg/day. Decreased growth of offspring was observed at 500 mg/kg/day and higher (approximately 38 times the maximum reported human maintenance dose [100 mg/kg/day] based on AUC) and reduction in offspring survival during lactation was observed at 2000 mg/kg/day (approximately 38 times the maximum reported human maintenance dose [100 mg/kg/day] based on AUC). No effects on physical and sexual development, learning and memory, or reproductive performance were observed through maturation of the surviving offspring at maternal doses up to 2000 mg/kg/day. The high dose (2000 mg/kg/day) produced maternal toxicity (impaired weight gain and approximately 10% mortality).

8.3 Nursing Mothers
It is not known whether CARBAGLU is excreted in human milk. Carglumic acid is excreted in rat milk, and an increase in mortality and impairment of body weight gain occurred in neonatal rats nursed by mothers receiving carglumic acid. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from CARBAGLU, breast-feeding is not recommended. Treatment is continuous and lifestyle-long for NAGS deficiency patients.

8.4 Pediatric Use
The efficacy of CARBAGLU for the treatment of hyperammonemia in patients with NAGS deficiency from birth to adulthood was evaluated in a retrospective review of the clinical course of 23 NAGS deficiency patients who all began CARBAGLU treatment during infancy or early childhood. There are no apparent differences in clinical response between adults and pediatric NAGS deficiency patients treated with CARBAGLU. However, data are limited.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Carglumic acid is a synthetic structural analogue of N-acetylglutamate (NAG) which is produced from glutamate and acetyl-CoA in a reaction catalyzed by N-acetylglutamate synthase (NAGS), a mitochondrial liver enzyme. NAG acts as an essential allosteric activator of Carbamoyl Phosphate Synthetase 1 (CPS 1), a mitochondrial liver enzyme which catalyzes the first reaction of the urea cycle. The urea cycle, whose role is the disposition of ammonia, includes a series of biochemical reactions in the liver resulting in the conversion of ammonia into urea, which is then excreted through the urine. Carglumic acid acts as a CPS1 activator in patients with NAGS deficiency, thereby removing the block in the urea cycle and facilitating ammonia detoxification and urea production.

12.2 Pharmacokinetics
In a retrospective review of the clinical course in 23 patients with NAGS deficiency, carglumic acid reduced plasma ammonia levels within 24 hours when administered with and without concomitant ammonia lowering therapies. No dose response relationship has been identified.

12.3 Pharmacokinetics
The pharmacokinetics of carglumic acid have been studied in healthy male subjects using both radiolabeled and non-radiolabeled carglumic acid.
The mean plasma ammonia level at baseline and the decline that is observed after treatment with CARBAGLU in 13 evaluable patients with NAGS deficiency is illustrated in Figure 1.

Figure 1: Ammonia response for 13 evaluable NAGS deficiency patients at baseline and after treatment with CARBAGLU

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied
CARBAGLU is a white and elongated 200 mg tablet for oral suspension, functionally scored and coded ‘C’ on one side. CARBAGLU is available in 5 or 60 tablets in a high density polyethylene bottle with child resistant polypropylene cap and desiccant unit.

NDC 52276-312-05 Bottles of 5 tablets
NDC 52276-312-60 Bottles of 60 tablets

Storage
Store in the original unopened container at 2 – 8°C (36 – 46°F).

After first opening of the container:
• Do not refrigerate, store at room temperature between 15 – 30°C (59 – 86°F).
• Keep the container tightly closed between openings in order to protect from moisture.
• Write the date of opening on the tablet container.
• Do not use after the expiration date stated on the tablet container.
• Discard one month after first opening.

17 PATIENT COUNSELING INFORMATION

Advises the patient to read the FDA-approved patient labeling (Instructions for Use).

Preparation and Administration
• Disperse CARBAGLU tablets in water. Do not swallow whole or crushed.
• Take CARBAGLU immediately before meals or feedings.
• CARBAGLU tablets dispersed in water can be administered orally or via a nasogastric tube, as described in the Instructions for Use.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
The carcinogenic potential of carglumic acid was assessed in a 2-year carcinogenicity study in rats. Carglumic acid was not tumorigenic at oral doses up to 1000 mg/kg/day (approximately 38 times the maximum reported human maintenance dose [100 mg/kg/day] based on AUC).

Carglumic acid was negative in the Ames test, chromosomal aberration assay in human lymphocytes, and the in vivo micronucleus assay in rats.

13.2 Pregnancy
The effect of carglumic acid on human pregnancy has not been determined.

13.3 Lactation
It is not known if carglumic acid is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when CARBAGLU is administered to a nursing woman.

13.4 Pediatric Use
There are no adequate and well-controlled studies in pregnant women or in patients aged <16 years. However, carglumic acid was safe and well tolerated in patients with NAGS deficiency aged 1 to 16 years in a large, open-label, multinational, nonrandomized, multicenter study. Therefore, use of CARBAGLU in pregnant women or in pediatric patients has not been determined.

13.5 Geriatric Use
There is no information on patients aged 65 years and older.

13.6 Other Populations
No drug interaction studies have been performed. Based on in vitro studies, CARBAGLU is not an inducer of CYP1A1/2, CYP2B6, CYP2C, and CYP3A4/5 enzymes, and not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2D6, CYP2C9, CYP2D6, CYP2E1, and CYP3A4/5 enzymes.

14 CLINICAL STUDIES

14.1 Responses of Patients with NAGS Deficiency to Acute and Chronic Treatment
The efficacy of CARBAGLU in the treatment of hyperammonemia due to NAGS deficiency was evaluated in a retrospective review of the clinical course of 23 NAGS deficiency patients who received CARBAGLU treatment for a median of 7.9 years (range 0.6 to 20.8 years). Treatment with CARBAGLU was divided in two regimens. For acute treatment, the dosage was reduced over time based upon biochemical and clinical responses. The demographics characteristics of the patient population are shown in Table 2.

Table 2. Baseline Characteristics of the 23 NAGS deficiency patients

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>Age at initiation of CARBAGLU therapy (years) Mean (SD)</th>
<th>Age groups at initiation of CARBAGLU therapy</th>
<th>NAGS gene mutations by DNA testing</th>
<th>Patients current treatment status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>14 (61%)</td>
<td>9 (39%)</td>
<td>Mean (SD) 2 (4)</td>
<td>Min-Max 0-13</td>
<td>homozgyous 14 (61%)</td>
<td>On-going 18 (78%)</td>
</tr>
<tr>
<td>Age groups at initiation of CARBAGLU therapy</td>
<td>&lt; 30 days 9 (39%)</td>
<td>&gt;30 days – 11 months 9 (39%)</td>
<td>&gt;1 - 13 years 5 (22%)</td>
<td>Not available 5 (22%)</td>
<td>Not available 5 (22%)</td>
<td></td>
</tr>
<tr>
<td>NAGS gene mutations by DNA testing</td>
<td>heterozygous 4 (17%)</td>
<td>Not available 5 (22%)</td>
<td>On-going 18 (78%)</td>
<td>Not available 5 (22%)</td>
<td>Not available 5 (22%)</td>
<td></td>
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<td>Not available 5 (22%)</td>
<td></td>
</tr>
</tbody>
</table>

14.2 Long-term Efficacy
The efficacy of CARBAGLU was divided in two regimens. For chronic treatment, the long-term efficacy was evaluated in a retrospective review of the clinical course of 23 NAGS deficiency patients who received treatment with CARBAGLU for a median of 7.9 years (range 0.6 to 20.8 years). Treatment with CARBAGLU was divided in two regimens. For acute treatment, the dosage was reduced over time based upon biochemical and clinical responses. The demographics characteristics of the patient population are shown in Table 2.

Table 3. Plasma ammonia levels at baseline and after treatment with CARBAGLU

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Statistics (N = 13)</th>
<th>Ammonia** (micromol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Mean (SD) 271 (359)</td>
<td>13</td>
</tr>
<tr>
<td>Day 1</td>
<td>Mean (SD) 181 (358)</td>
<td>10</td>
</tr>
<tr>
<td>Day 2</td>
<td>Mean (SD) 69 (78)</td>
<td>8</td>
</tr>
<tr>
<td>Day 3</td>
<td>Mean (SD) 27 (11)</td>
<td>25</td>
</tr>
</tbody>
</table>

* 13/23 patients with complete short-term and long-term plasma ammonia documentation
** Mean ammonia normal range: 5 to 50 micromol/L
**Storage**
- Store UNOPENED container in a refrigerator at 2 to 8°C (36 to 46°F). After first opening of the container: do not refrigerate, store at room temperature between 15 to 30°C (59 to 86°F). Keep the container tightly closed in order to protect from moisture. Write the date of opening on the tablet container. Discard one month after first opening. Do not use after the expiration date stated on the tablet container.

**Lactation**
- Advise women not to breast-feed during treatment with CARBAGLU [see Use in Specific Populations (8.3)].

**Supplied by:**
Orphan Europe SARL
Puteaux, France

---

**Licensed to and Distributed by:**
Recordati Rare Diseases Inc.
Lebanon, NJ 08833

For drug or ordering information please call Accredo Health Group Inc., Customer Service at 1-888-464-8860.

**Carbaglu®** is a licensed trademark of Recordati Rare Diseases Inc.
This product label may have been updated. For the most recent prescribing information, please visit www.recordatirarediseases.com or www.carbaglu.net.
INSTRUCTIONS FOR USE
CARBAGLU (CAR-buh-gloo)
carbgluic acid) tablet for oral suspension

Important information:
• CARBAGLU tablet for oral suspension (CARBAGLU tablet) must be mixed in water before taking. CARBAGLU tablets should not be mixed in any other food or liquid.
• Do not swallow CARBAGLU tablets whole.
• Do not crush CARBAGLU tablets.
• Take CARBAGLU right before meals or feedings.
• The CARBAGLU tablet and water mixture has a slightly sour taste.

You may need to ask your healthcare provider or pharmacist for a medicine cup to measure the correct amount of water you will need to prepare your dose of CARBAGLU.

Taking CARBAGLU tablets by mouth using a cup:

Children and Adults
1. Add about 2.5 mL of water into a small cup for each CARBAGLU tablet, or each ¼ CARBAGLU tablet, needed for the prescribed dose. For example, if the prescribed dose is 2 CARBAGLU tablets, add about 5 mL of water into the cup. If the prescribed dose is 2½ CARBAGLU tablets, add about 7.5 mL of water into the cup. Ask your healthcare provider if you are not sure of how much water you should use for the prescribed dose of CARBAGLU.
2. Place the prescribed number of CARBAGLU tablets into the water in the cup.
3. Carefully stir the CARBAGLU tablet and water mixture in the cup to avoid spilling the mixture. CARBAGLU tablets do not dissolve completely in water.
4. Swallow the CARBAGLU tablet and water mixture right away.
5. Pieces of the tablet may remain in the cup. Add more water to the cup to rinse the cup and swallow the mixture right away.
6. Repeat step 5 until there are no pieces of the tablet left in the cup.

Taking CARBAGLU tablets by mouth using an oral syringe:

Children
1. Add about 2.5 mL of water into a small cup for each CARBAGLU tablet, or each ¼ CARBAGLU tablet, needed for the prescribed dose. For example, if the prescribed dose is 2 CARBAGLU tablets, add about 5 mL of water into the cup. If the prescribed dose is 2½ CARBAGLU tablets, add about 7.5 mL of water into the cup. Ask your healthcare provider if you are not sure of how much water you should use for the prescribed dose of CARBAGLU.
2. Place the prescribed number of CARBAGLU tablets into the water in the cup.
3. Carefully stir the CARBAGLU tablet and water mixture in the cup to avoid spilling the mixture. CARBAGLU tablets do not dissolve completely in water.
4. Draw up all of the CARBAGLU tablet and water mixture in the cup into a catheter-tip syringe.
5. Connect the catheter-tip syringe to the NG tube.
6. Give the CARBAGLU tablet and water mixture through the NG tube right away.
7. Pieces of the tablet may remain in the catheter-tip syringe or NG tube. Refill the catheter-tip syringe with 1 mL to 2 mL of water and flush the NG tube right away.
8. Repeat step 7 until there are no pieces of the tablet left in the catheter-tip syringe or NG tube.

Giving CARBAGLU tablets through a nasogastric (NG) tube:

Children and Adults
1. Add about 2.5 mL of water into a small cup for each CARBAGLU tablet, or each ½ CARBAGLU tablet, needed for the prescribed dose. For example, if the prescribed dose is 2 CARBAGLU tablets, add about 5 mL of water into the cup. If the prescribed dose is 2½ CARBAGLU tablets, add about 7.5 mL of water into the cup. Ask your healthcare provider if you are not sure of how much water you should use for the prescribed dose of CARBAGLU.
2. Place the prescribed number of CARBAGLU tablets into the water in the cup.
3. Carefully stir the CARBAGLU tablet and water mixture in the cup to avoid spilling the mixture. CARBAGLU tablets do not dissolve completely in water.
4. Draw up all of the CARBAGLU tablet and water mixture into the NG tube. Refill the catheter-tip syringe with 1 mL to 2 mL of water and flush the NG tube right away.
5. Connect the catheter-tip syringe to the NG tube.
6. Give the CARBAGLU tablet and water mixture through the NG tube right away.
7. Pieces of the tablet may remain in the catheter-tip syringe or NG tube. Refill the catheter-tip syringe with 1 mL to 2 mL of water and flush the NG tube right away.
8. Repeat step 7 until there are no pieces of the tablet left in the catheter-tip syringe or NG tube.

How should I store CARBAGLU?
• Before opening, store CARBAGLU in a refrigerator between 36°F to 46°F (2°C to 8°C) in the container it comes in.
• After opening, store CARBAGLU at room temperature between 59°F to 86°F (15°C to 30°C). Do not store CARBAGLU in a refrigerator.
  - Keep CARBAGLU tablets in a tightly closed container to protect the tablets from moisture.
  - Write the date the CARBAGLU tablet container is opened on the container label. Throw away any unused tablets one month after opening the tablet container.
• Do not use CARBAGLU tablets after the expiration date on the tablet container.

Keep CARBAGLU and all medicines out of the reach of children.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

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