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 for the treatment of acute hyperammonemia due to the deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS). (1.1)
- Maintenance therapy for the treatment of 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.
- Monitor plasma ammonia and adjust the dosage to maintain the level within the normal range for age.

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.

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

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

----------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 reduce plasma ammonia level is essential. (5.1)

----------ADVERSE REACTIONS----------

Most common adverse reactions (>9%) are: vomiting, abdominal pain, pyrexia, tonsillitis, anemia, diarrhea, ear infection, infections, nasopharyngitis, hemoglobin decreased, and headache (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: 12/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

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). 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.

1.2 Chronic Hyperammonemia in Patients with NAGS Deficiency

CARBAGLU is indicated as maintenance therapy in pediatric and adult patients for the treatment of chronic hyperammonemia due to 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.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

CARBAGLU should be initiated as soon as the diagnosis of NAGS deficiency is suspected, which may be as soon as at birth, and managed by a physician and medical team experienced in metabolic disorders.

Initial Dosage: The recommended initial daily dosage of CARBAGLU in pediatric and adult patients for acute hyperammonemia is 100 mg/kg to 250 mg/kg divided into 2 to 4 doses and rounded to the nearest 100 mg (i.e., half of a CARBAGLU tablet). Concomitant administration of other ammonia lowering therapies is recommended.

Maintenance Dosage: The recommended daily maintenance dosage of CARBAGLU in pediatric and adult patients is 10 mg/kg to 100 mg/kg divided into 2 to 4 doses and rounded to the nearest 100 mg (i.e., half of a CARBAGLU tablet).

Therapeutic Monitoring: Closely monitor plasma ammonia levels. Titrate the CARBAGLU dosage to maintain the plasma ammonia level within the normal range for the patient's age, taking into consideration their clinical condition (e.g., nutritional requirements, protein intake, growth parameters, etc.).

2.2 Preparation and Administration

- *Disperse CARBAGLU tablets in water. Do not swallow whole or crushed.*
- Mix each 200 mg tablet in a minimum of 2.5 mL of water to yield a concentration of 80 mg/mL.

- CARBAGLU tablets do not dissolve completely in water and undissolved particles of the tablet may remain in the mixing container.
- Take CARBAGLU immediately before meals or feedings.
- The CARBAGLU suspension has a slightly acidic taste.
- For all preparations, use in foods or liquids, other than water, has not been studied clinically and is not recommended.

Preparation for Oral Administration in Pediatric and Adult Patients

- 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.
- Swallow the mixture immediately. Pieces of the tablet may remain in the cup.
- Rinse the cup with additional water and swallow the mixture immediately. Repeat as needed until no pieces of the tablet are left in the cup.

Preparation for Nasogastric Tube Administration in Pediatric and Adult Patients

For patients who have a nasogastric tube in place, 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 into a catheter-tip syringe.
- Administer the mixture immediately through the nasogastric (NG) tube. Pieces of the tablet may remain in the catheter-tip syringe or NG tube.
- 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 Pediatric 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.

4 CONTRAINDICATIONS

None

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.

Table 1 summarizes adverse reactions occurring in 2 or more patients treated with CARBAGLU in the retrospective case series (≥ 9%).

Table 1: Adverse Reactions Reported in ≥ 2 Patients in the Retrospective Case Series Treated with CARBAGLU

Adverse Reaction	Number of Patients (N) (%)
Vomiting	6 (26)

Adverse Reaction	Number of Patients (N) (%)
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)
Hemoglobin decreased	3 (13)
Headache	3 (13)
Dysgeusia	2 (9)
Asthenia	2 (9)
Hyperhidrosis	2 (9)
Influenza	2 (9)
Pneumonia	2 (9)
Weight decreased	2 (9)
Anorexia	2 (9)
Somnolence	2 (9)
Rash	2 (9)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Although rare case reports of CARBAGLU use in pregnant women are insufficient to inform a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes, untreated NAGS deficiency can result in irreversible neurologic damage and death in pregnant women *[see Warnings and Precautions (5.1) and Clinical Considerations]*.

In an animal reproduction study, decreased survival and growth occurred in offspring born to rats that received carglumic acid at a dose approximately 38 times the maximum reported human maintenance dose.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, miscarriage, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%,

respectively.

There is a pregnancy pharmacovigilance program for CARBAGLU. If CARBAGLU is administered during pregnancy, health care providers should report CARBAGLU exposure by calling 1-888-575-8344.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Pregnant women with urea cycle disorders may experience an increase in catabolic stress which can trigger a hyperammonemic crisis both in the intrapartum and in the post-partum (3-14 days post-partum) periods. Maternal complications related to hyperammonemic crisis can include neurological impairment, coma and in some cases death.

Data

Animal Data

No effects on embryo-fetal 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) during organogenesis.

In a pre- 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).

8.2 Lactation

Risk Summary

It is not known whether carglumic acid is present in human milk. There are no available data on the effects of carglumic acid on the breastfed infant or the effects on milk production. Carglumic acid is present in milk from treated rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CARBAGLU and any potential adverse effects on the breastfed child

from CARBAGLU or from the underlying maternal condition.

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 childhood. There are no apparent differences in clinical response between adults and pediatric NAGS deficiency patients treated with CARBAGLU. However, data are limited.

8.5 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.

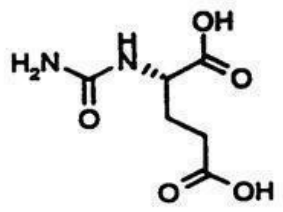
Repeated oral dosing of carglumic acid at 2000 mg/kg/day was lethal to most neonatal rats within 2-3 days of treatment. The plasma concentrations that produced lethality were not measured. In adult rats, a single oral administration of carglumic acid was not lethal at doses up to 2800 mg/kg (approximately 20 times the maximum starting dose based on C_{max}).

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) pentanedioic acid, with a molecular weight of 190.16.

The structural formula is:



Molecular Formula: $C_6H_{10}N_2O_5$

The inactive ingredients of CARBAGLU are croscarmellose sodium, hypromellose, microcrystalline cellulose, silica colloidal anhydrous, sodium lauryl sulfate, sodium stearyl fumarate.

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 Pharmacodynamics

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.

Absorption

The median T_{max} of CARBAGLU was 3 hours (range: 2 to 4 hours). Absolute bioavailability has not been determined.

Distribution

The apparent volume of distribution was 2657 L (range: 1616-5797). Protein binding has not been determined.

Elimination

Metabolism

A proportion of carglumic acid may be metabolized by the intestinal bacterial flora. The likely end product of carglumic acid metabolism is carbon dioxide, eliminated through the lungs.

Excretion

Median value for the terminal half-life was 5.6 hours (range 4.3 to 9.5 hours), the apparent total clearance was 5.7 L/min (range 3.0 to 9.7 L/min), the renal clearance was 290 mL/min (range 204 to 445 mL/min), and the 24-hour urinary excretion was 4.5% of the dose (range 3.5 to 7.5%). Following administration of a single radiolabeled oral dose of 100 mg/kg of body weight, 9% of the dose was excreted unchanged in the urine and up to 60% of the dose was excreted unchanged in the feces.

Drug Interaction Studies

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, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5 enzymes.

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 34 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.

There were no effects on fertility or reproductive performance in female rats at oral doses up to 2000 mg/kg/day (approximately 38 times the maximum reported human maintenance dose [100 mg/kg/day] based on AUC). In a separate study, mating and fertility were unaffected in male rats at oral doses up to 1000 mg/kg/day (approximately 34 times the maximum reported human maintenance dose [100 mg/kg/day] based on AUC).

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, patients received a total daily dose of 100 to 250 mg/kg per day primarily administered in 2 to 4 divided doses for the first few days of treatment. For maintenance 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

		Patients N=23
Gender	Male	14 (61%)
	Female	9 (39%)
Age at initiation of CARBAGLU therapy (years)	Mean (SD)	2 (4)
	Min-Max	0-13
Age groups at initiation of CARBAGLU therapy	<30 days	9 (39%)
	>30 days - 11 months	9 (39%)
	≥1 - 13 years	5 (22%)
NAGS gene mutations by DNA testing	homozygous	14 (61%)
	heterozygous	4 (17%)
	Not available	5 (22%)
Patients current treatment status	On-going	18 (78%)
	Discontinued	5 (22%)

The clinical observations in the 23 patient case series were retrospective, unblinded and uncontrolled and preclude any meaningful formal statistical analyses of the data. However, short-term efficacy was evaluated using mean and median change in plasma ammonia levels from baseline to days 1 to 3. Persistence of efficacy was evaluated using long-term mean and median change in plasma ammonia level. Table 3 summarizes the plasma ammonia levels at baseline, days 1 to 3 post-CARBAGLU treatment, and long-term CARBAGLU treatment for 13 evaluable patients. Of the 23 NAGS deficiency patients who received treatment with CARBAGLU, a subset of 13 patients who had both well documented plasma ammonia levels prior to CARBAGLU treatment and after long-term treatment with CARBAGLU were selected for analysis.

All 13 patients had abnormal ammonia levels at baseline. The overall mean baseline plasma ammonia level was 271 micromol/L. By day 3, normal plasma ammonia levels were attained in patients for whom data were available. Long-term efficacy was measured using the last reported plasma ammonia level for each of the 13 patients analyzed (median length of treatment was 6 years; range 1 to 16 years). The mean and median ammonia levels were 23 micromol/L and 24 micromol/L, respectively, after a mean treatment duration of 8 years.

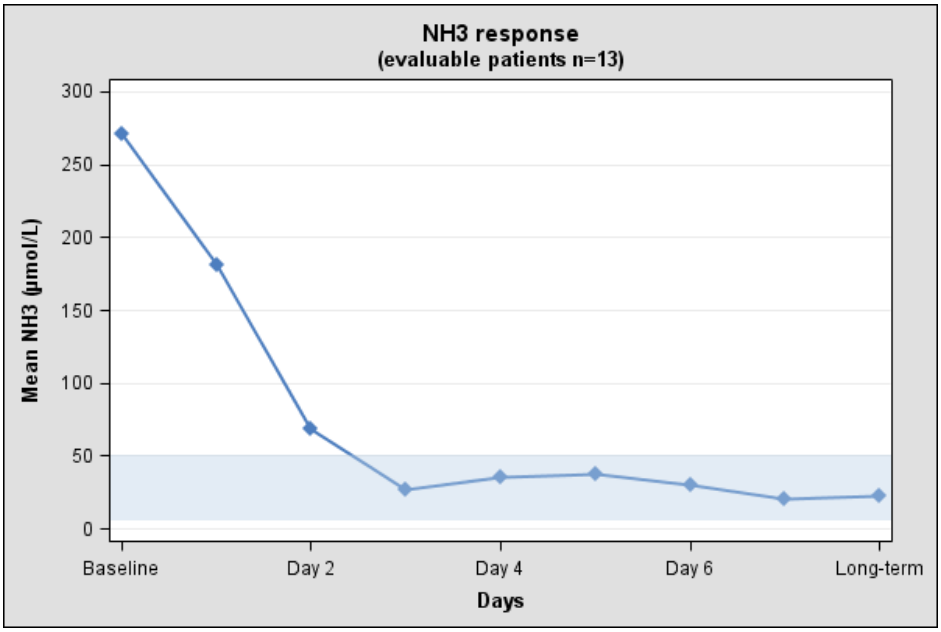
Table 3: Plasma ammonia levels at baseline and after treatment with CARBAGLU

Timepoint	Statistics (N = 13*)	Ammonia** (micromol/L)
Baseline (prior to first treatment with CARBAGLU)	N	13
	Mean (SD)	271 (359)
	Median	**157**
	Range	72-1428
	Missing Data	0
Day 1	N	10
	Mean (SD)	181 (358)
	Median	**65**
	Range	25-1190
	Missing Data	3
Day 2	N	8
	Mean (SD)	69 (78)
	Median	**44**
	Range	11-255
	Missing Data	5
Day 3	N	5
	Mean (SD)	27 (11)
	Median	**25**
	Range	12-42
	Missing Data	8
Long-term Mean: 8 years Median: 6 years 1 to 16 years (last available value on CARBAGLU treatment)	N	13
	Mean (SD)	23 (7)
	Median	**24**
	Range	9-34
	Missing Data	0

* 13/23 patients with complete short-term and long-term plasma ammonia documentation
** Mean ammonia normal range: 5 to 50 micromol/L

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

Advise 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 CARBABLU 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 Us*e.

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.

Pregnancy

- Advise women who are exposed to CARBAGLU during pregnancy that there is a pregnancy surveillance program that monitors pregnancy outcomes *[see Use in Specific Populations (8.1)]*.

Supplied by:

Recordati Rare Diseases
Puteaux, France

Licensed to and Distributed by:

Recordati Rare Diseases Inc.
Lebanon, NJ 08833

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Carbaglu carglumic acid

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