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
Initial U.S. Approval: 2010

----------INDICATIONS AND USAGE----------
Carbaglu (carglumic acid) is a Carbamoyl Phosphate Synthetase 1 (CPS 1) activator indicated 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----------
Carbaglu treatment should be initiated by a physician experienced in metabolic disorders
Adult Dosage and Administration

- Recommended initial dose range for acute hyperammonemia is 100 mg/kg/day to 250 mg/kg/day. (2.1)
- Adjust dose to maintain normal plasma ammonia levels based on age. (2.1)
- Divide the total daily dose into two to four doses to be given immediately before meals or feedings. (2.1)
- Each divided dose should be rounded to the nearest 100 mg. (2.1)
- Each 200 mg tablet should be dispersed in a minimum of 2.5 ml of water and taken immediately. (2.2)
- Carbaglu can be administered orally or through a nasogastric tube. (2.3)
- Carbaglu tablets should not be swallowed whole or crushed. (2.2)

Pediatric Dosage and Administration

- Recommended initial dose range for acute hyperammonemia is 100 mg/kg/day to 250 mg/kg/day. (2.4)
- Divide the total daily dose into two to four doses to be given immediately before meals or feedings. (2.4)
- Mix each 200 mg tablet in 2.5 ml of water to yield a concentration of 80 mg/mL. (2.5)
- Carbaglu may be administered orally with an oral syringe or through a nasogastric tube. (2.5, 2.6)
- Carbaglu tablets should not be swallowed whole or crushed. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
200 mg tablets, scored (3)

----------CONTRAINDICATIONS----------
None. (4)

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

Therapeutic Monitoring: Plasma ammonia levels should be maintained within normal range for age via individual dose adjustment. (5.2)

Nutritional Management: In the initial treatment of NAGS deficiency, protein restriction is recommended. When plasma ammonia level is normalized, dietary protein intake can usually be reintroduced. (5.3)

----------ADVERSE REACTIONS----------
The most common adverse reactions in ≥ 13% of patients are: infections, vomiting, abdominal pain, pyrexia, tonsilitis, anemia, ear infection, diarrhea, nasopharyngitis, and headache (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact (Orphan Europe) at (1-877-894-0312), or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------
No drug interaction studies have been conducted (7)

----------USE IN SPECIFIC POPULATIONS----------
Pregnancy: No human data; decreased survival and growth in animal offspring. (8.1)

Nursing Mothers: Human milk-feeding is not recommended. (8.3)

See 17 for PATIENT COUNSELING INFORMATION
Revised: March/2010

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 are recommended.

1.2 Maintenance therapy for chronic hyperammonemia in patients with NAGS deficiency

Carbaglu is indicated for maintenance therapy in pediatric and adult patients for 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 reduced or discontinued based on plasma ammonia levels.

2 DOSAGE AND ADMINISTRATION

Carbaglu treatment should be initiated by a physician experienced in metabolic disorders.

2.1 Adult Dosage and Administration

The recommended initial dose for acute hyperammonemia is 100 mg/kg/day to 250 mg/kg/day. Concomitant administration of other ammonia lowering therapies is recommended. Dosing should be titrated based on individual patient plasma ammonia levels and clinical symptoms.

The recommended maintenance dose should be titrated to target normal plasma ammonia level for age. Based on limited data in 22 patients receiving maintenance treatment with Carbaglu in a retrospective case series, maintenance doses were usually less than 100 mg/kg/day.

The total daily dose should be divided into 2 to 4 doses and rounded to the nearest 100 mg. (i.e. half a Carbaglu Tablet)

2.2 Preparation for Oral Administration in Adults

Carbaglu tablets should not be swallowed whole or crushed. Disperse Carbaglu tablets in water immediately before use.

Each 200 mg tablet should be dispersed in a minimum of 2.5 ml of water and taken immediately. Carbaglu tablets do not dissolve completely in water and undissolved particles of the tablet may remain in the mixing container.

To ensure complete delivery of the dose, the mixing container should be rinsed with additional volumes of water and the contents swallowed immediately.

USE IN OTHER FOODS AND LIQUIDS HAS NOT BEEN STUDIED CLINICALLY AND IS THEREFORE NOT RECOMMENDED.

2.3 Preparation for Nasogastric Tube Administration in Adults

For patients who have a nasogastric tube in place, Carbaglu should be administered as follows:

- Mix each 200 mg tablet in a minimum of 2.5 ml of water. Shake gently to allow for quick dispersal.
- Administer the dispersion immediately through the nasogastric tube
- Flush with additional water to clear the nasogastric tube.

2.4 Pediatric Dosage and Administration

The recommended initial dose for acute hyperammonemia is 100 mg/kg/day to 250 mg/kg/day. Concomitant administration of other ammonia lowering therapies is recommended. Dosing should be titrated based on individual patient plasma ammonia levels and clinical symptoms.

The recommended maintenance dose should be titrated to target normal plasma ammonia level for age. Based on limited data in 22 patients receiving maintenance treatment with Carbaglu in a retrospective case series, maintenance doses were usually less than 100 mg/kg/day.

The total daily dose should be divided into 2 to 4 doses.

2.5 Preparation for Oral Administration Using an Oral Syringe in Pediatrics

For administration via oral syringe, Carbaglu should be administered as follows:

- Mix each 200 mg tablet in 2.5 ml of water to yield a concentration of 80 mg/mL in a mixing container. Shake gently to allow for quick dispersal.
- Draw up the appropriate volume of dispersion in an oral syringe and administer immediately. Discard the unused portion.
- Refill the oral syringe with a minimum volume of water (1-2 mL) and administer immediately.

2.6 Preparation for Nasogastric Tube Administration in Pediatrics

For patients who have a nasogastric tube in place, Carbaglu should be administered as follows:

- Mix each 200 mg tablet in 2.5 ml of water to yield a concentration of 80 mg/mL in a mixing container. Shake gently to allow for quick dispersal.
- Draw up the appropriate volume of dispersion and administer immediately through a nasogastric tube. Discard the unused portion.
- Flush with additional water to clear the nasogastric tube.

3 DOSAGE FORMS AND STRENGTHS

Carbaglu is a white and elongated 200 mg tablet, 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 hyperammonemia may require dialysis, preferably hemodialysis, to remove a large burden of ammonia. Uncontrolled hyperammonemia can rapidly result in brain injury/damage or death, and prompt use of all therapies necessary to reduce plasma ammonia levels is essential.

Management of hyperammonemia due to NAGS deficiency should be done in coordination with medical personnel experienced in metabolic disorders. Ongoing monitoring of plasma ammonia levels, neurological status, laboratory tests and clinical responses in patients receiving Carbaglu is crucial to assess patient response to treatment.

5.2 Therapeutic Monitoring

Plasma ammonia levels should be maintained within normal range for age via individual dose adjustment.

5.3 Nutritional Management

During acute hyperammonemic episodes, protein restriction and hypercaloric intake is recommended to block ammonia generating catabolic pathways. When plasma ammonia levels have normalized, protein intake can usually be increased with the goal of unrestricted protein intake.

6 ADVERSE REACTIONS

6.1 Retrospective Case Series Experience

The most common adverse reactions (occurring in ≥ 13% of patients), regardless of causality, are: vomiting, abdominal pain, pyrexia, tonsilitis, anemia, ear infection, diarrhea, nasopharyngitis, and headache.

Table 1 summarizes adverse reactions occurring in 2 or more patients treated with Carbaglu in the retrospective case series. Because these reactions were reported retrospectively, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Table 1: Adverse Reactions Reported in ≥ 2 Patients in the Retrospective Case Series treated with Carbaglu

System Organ Class Preferred Term	**Number of Patients (N)(%)**
TOTAL	**23 (100)**
Blood and lymphatic system disorders	
Anemia	3 (13)
Ear and labyrinth disorders	
Ear infection	3 (13)
Gastrointestinal disorders	
Abdominal pain	4 (17)
Diarrhea	3 (13)
Vomiting	6 (26)
Dysgeusia	2 (9)
General disorders and administration site conditions	
Asthenia	2 (9)
Hyperhidrosis	2 (9)
Pyrexia	4 (17)
Infections and infestations	
Infection	3 (13)
Influenza	2 (9)
Nasopharyngitis	3 (13)
Pneumonia	2 (9)
Tonsillitis	4 (17)
Investigations	
Hemoglobin decreased	3 (13)
Weight decreased	2 (9)
Metabolism and nutrition disorders	
Anorexia	2 (9)
Nervous system disorders	
Headache	3 (13)
Somnolence	2 (9)
Skin and subcutaneous tissue disorders	
Rash	2(9)

7 DRUG INTERACTIONS

No drug interaction studies have been performed.

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 doses similar to the maximum recommended starting human dose during pregnancy and lactation. Because untreated N-acetylglutamate synthase (NAGS) deficiency results in irreversible neurologic damage and death, women with NAGS must remain on treatment throughout pregnancy. In embryo-fetal developmental toxicity studies, pregnant rats and rabbits received oral carglumic acid during organogenesis at doses up to 1.3 times the maximum recommended human starting dose based on body surface area (mg/m^2). Actual doses were 500 and 2000 mg/kg/day (rats) and 250 and 1000 mg/kg/day (rabbits). The high doses resulted in maternal toxicity in both rats and rabbits. No effects on embryo-fetal development were observed in either species.

In a peri- and post-natal developmental study, female rats received oral carglumic acid from organogenesis through day 21 post-partum at doses up to 1.3 times the maximum recommended starting human dose based on body surface area (mg/m^2). Actual doses were 500 and 2000 mg/kg/day. A reduction in offspring survival was seen at the high dose and a reduction in offspring growth was seen at both doses.

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, human milk-feeding is not recommended. Treatment is continuous and life-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 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.

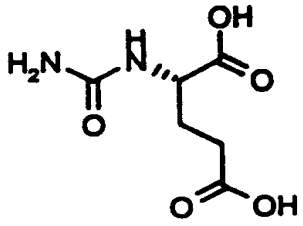
Repeated oral dosing of carglumic acid at 2000 mg/kg/day was lethal to most neonatal rats within 2-3 days of treatment. In adult rats, a single oral administration of carglumic acid was not lethal at doses up to 2800 mg/kg (1.8 times the maximum recommended starting dose based on a body surface area comparison to adult humans).

11 DESCRIPTION

Carbaglu tablets for oral administration 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, 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 microcrystalline cellulose, sodium lauryl sulfate, hypromellose, croscarmellose sodium, silica colloidal anhydrous, sodium stearyl fumarate.

CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Carglumic acid is a synthetic structural analogue of N-acetylglutamate (NAG), which is an essential allosteric activator of carbamoyl phosphate synthetase 1 (CPS 1) in liver mitochondria. CPS 1 is the first enzyme of the urea cycle, which converts ammonia into urea. NAG is the product of N-acetylglutamate synthase (NAGS), a mitochondrial enzyme. Carglumic acid acts as a replacement for NAG in NAGS deficiency patients by activating CPS 1.

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 has been studied in healthy male volunteers using both radiolabeled and non-radiolabeled carglumic acid.

Absorption

The median Tmax of Carbaglu was 3 hours (range: 2-4). Absolute bioavailability has not been determined.

Distribution

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

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.

Elimination

Median values for the terminal half-life was 5.6 hours (range 4.3-9.5), the apparent total clearance was 5.7 L/min (range 3.0-9.7), the renal clearance was 290 mL/min (range 204-445), and the 24-hour urinary excretion was 4.5 % of the dose (range 3.5-7.5). 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been performed with carglumic acid.

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 (1.3 times the maximum recommended human starting dose based on body surface area). In a separate study, mating and fertility were unaffected in male rats at oral doses up to 1000 mg/kg/day (0.6 times the maximum recommended human starting dose based on body surface area).

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).

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 month	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 µmol/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 µmol/L and 24 µmol/L, respectively, after a mean treatment duration of 8 years.

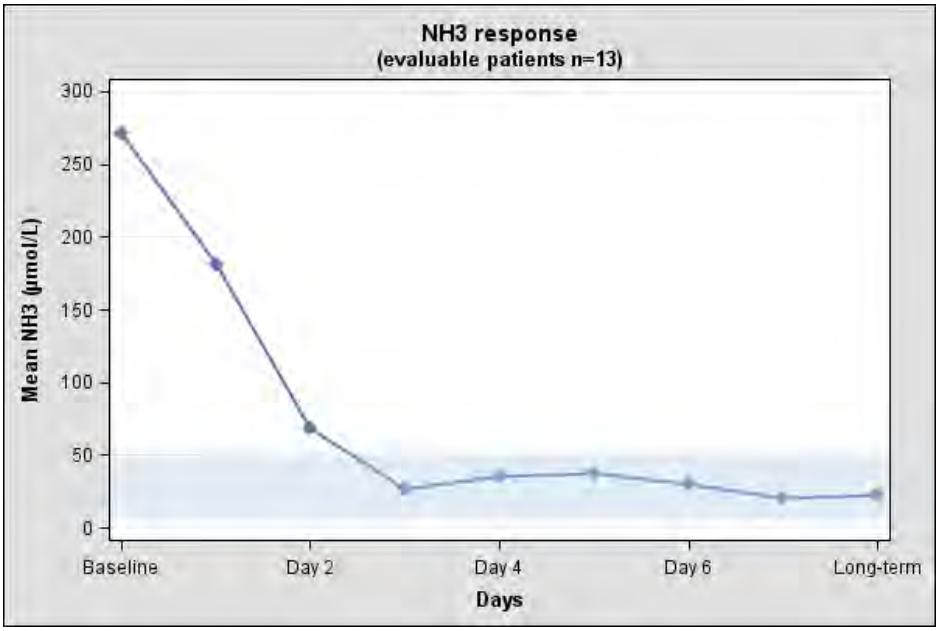
Table 3: Plasma ammonia levels at baseline and after treatment with Carbaglu

Timepoint	Statistics (N = 13*)	Ammonia** (µmol/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 µmol/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 tablet, scored and coded “C” on one side.

Each tablet contains 200 mg of carglumic acid. Carbaglu is available in 5 or 60 tablets in a polypropylene bottle with polyethylene cap and desiccant unit.

NDC XXXXXXX Bottles of 5 tablets

NDC XXXXXXX Bottles of 60 tablets

Storage

Before opening, store refrigerated at 2 - 8°C (36 – 46°F).

After first opening of the container:

- Do not refrigerate, do not store above 30°C (86° F).
- Keep the container tightly closed 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

Physicians should inform patients and caregivers about the following instructions for safe use of Carbaglu:

- Carbaglu tablets should not be swallowed whole or crushed. Each tablet should be dispersed in a minimum of 2.5 mL of water. Carbaglu tablets do not dissolve completely in water and undissolved particles of the tablet may remain in the mixing container. The mixing container should be rinsed with additional volumes of water and the contents swallowed immediately.
- Before opening, store in a refrigerator 2 to 8 ^{o}C (36 to 46 ^{o}F).
- Keep the container tightly closed in order to protect from moisture.
- After first opening of the container: do not refrigerate, do not store above 30 °C (86 °F).
- 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.

Physicians should also advise patients and caregivers that:

- When plasma ammonia levels have normalized, dietary protein intake can usually be increased with the goal of unrestricted protein intake.
- Human milk-feeding is not recommended.
- The most common adverse reactions are vomiting, abdominal pain, pyrexia, tonsilitis, anemia, ear infection, diarrhea, nasopharyngitis, and headache.

Manufactured By: Orphan Europe SARL, Paris, France