PRODUCT MONOGRAPH

[Pr]Carbaglu®

Carglumic acid dispersible tablets

200 mg

amino acids and derivatives

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Carbaglu®

Carglumic acid dispersible tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Dispersible tablets / 200 mg	Croscarmellose sodium, hypromellose, microcrystalline cellulose, silica colloidal anhydrous, sodium laurilsulfate, sodium stearyl fumarate.

INDICATIONS AND CLINICAL USE

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.

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-aceytlglutamate 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.

CONTRAINDICATIONS

- Hypersensitivity to carglumic acid or to any ingredient in the formulation. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.

- Breastfeeding during the use of Carbaglu (see WARNINGS AND PRECAUTIONS).

WARNINGS AND PRECAUTIONS

General
Any episode of acute symptomatic hyperammonemia should be treated as a life-threatening emergency. 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. Treatment of hyperammonemia may require dialysis, preferably hemodialysis, to remove a large burden of ammonia.

Management of hyperammonemia due to NAGS deficiency should be done in coordination with medical personnel experienced in metabolic disorders.

Endocrine and Metabolism
Since hyperammonemia is the result of protein catabolism, complete protein restriction is recommended to be maintained for 24 to 48 hours and caloric supplementation should be maximized to reverse catabolism and nitrogen turnover. When plasma ammonia levels have normalized, protein intake can usually be increased with the goal of unrestricted protein intake.

Neurologic
Uncontrolled hyperammonemia can rapidly result in brain injury/damage or death.

Special Populations
Pregnant Women: There are no adequate and well controlled studies or available human data with Carbaglu in pregnant women. Caution should be exercised when prescribing to pregnant women.

Nursing Women: Because of the potential for serious adverse reactions in nursing infants from Carbaglu, breast-feeding is contraindicated. It is unknown if 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 (see TOXICOLOGY - Reproduction and Development).

Pediatrics (≤ 18 years of age): There are no apparent differences in clinical response between adults and pediatric NAGS deficiency patients treated with Carbaglu.

Geriatrics (≥ 65 years of age): Carbaglu has not been studied in the geriatric population. Therefore, the safety and effectiveness in geriatric patients have not been established.

Monitoring and Laboratory Tests
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. Plasma ammonia levels should be maintained within normal range for age through individual dose adjustment.

Monitoring of liver, renal, cardiac and haematological parameters is recommended due to the limited safety data available.

ADVERSE REACTIONS

Adverse Drug Reactions Overview

From clinical study data, the most common adverse events (AEs) observed with Carbaglu were infections, vomiting, abdominal pain, pyrexia, tonsillitis, anemia, ear infection, diarrhea, nasopharyngitis, and headache. The most common serious adverse events (SAEs) were vomiting, somnolence and pneumonia. There were two deaths in NAGS deficiency patients treated chronically with Carbaglu. The causes of death were multi-organ failure with encephalopathy in one patient and severe hyperammonemia following pneumonia in the second patient.

Clinical Trial Adverse Drug Reactions

Because a very limited number of patients were studied and the data were collected retrospectively, the adverse events reported may not provide a reliable reflection of potential adverse reactions associated with Carbaglu.

A Retrospective, non-comparative, descriptive review of data collected from NAGS deficiency patients treated with carglumic acid on a long-term basis was conducted to review the clinical and biological response of NAGS deficiency patients to carglumic acid within the first 7 days of treatment (short-term) and at the last report (long-term). A total of 23 confirmed NAGS deficiency patients (4 were determined to have a heterozygous NAG gene mutation) were identified. Seventeen out of the 23 patients had an adverse event (AE) reported (note: not all AEs may have been reported due to reliance on retrospective review of medical records for data collection). Two patients died due to an AE (a multi-organ failure with encephalopathy for the first one; a severe episode of hyperammonemia following a pneumonia for the other). In addition to the 2 above-mentioned patients, 9 other patients experienced a serious adverse event (SAE). In total, these non-fatal AEs are related mostly to two SOCs: 10 SAEs came from the gastrointestinal disorders SOC (the most frequent AE is “vomiting”, reported 6 times) and 10 SAEs came from the nervous system disorders SOC. In total, 118 AEs were reported, including 35 SAEs and 83 non-serious AEs. These AEs are mainly related to 3 SOC: 21% in gastrointestinal disorders, 19% in infections and infestations and 14% in nervous system disorders. The most common AEs (occurring in ≥ 13% of patients) are infections, vomiting, abdominal pain, pyrexia, tonsillitis, anemia, ear infection, diarrhea, nasopharyngitis, and headache. Adverse events occurring in 2 or more patients treated with Carbaglu in the retrospective case series are shown in Table 1.

Table 1: Adverse Events 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	6 (26)
Ear and labyrinth disorders	
Ear infection	3 (13)
Gastrointestinal disorders	
Abdominal pain	4 (17)
Diarrhea	3 (13)
Vomiting	6 (26)
Dysgueusia	2 (9)
General disorders and administration site conditions	
Asthenia	2(9)
Hyperhidrosis	2(9)
Pyrexia	4 (17)
Infection and infestations	
Infection	3(13)
Influenza	2(9)
Nasopharyngitis	3 (13)
Pneumonia	2 (9)
Tonsilitis	4 (17)
Investigations	
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)

Post-Market Adverse Drug Reactions

The following adverse events have been reported during post-marketing experience with Carbaglu. Because these events are reported voluntarily from a small patient population it is not always possible to reliably establish a causal relationship to drug exposure.

***Blood*:** eosinophilia, thrombocytopenia, WBC decreased;

***Cardiac disorders*:** restrictive cardiomyopathy, cardiac arrest, coagulopathy;

***Ear and labyrinth disorders*:** otitis media;

***Hepatobiliary disorders*:** ammonia increased, hepatic enzymes increased, hyperammonaemia;

***Infections and infestations*:** pneumonia, sepsis;

***Investigations*:** serum ferritin decreased, haemoglobin decreased;

Metabolism and nutrition disorder: acidosis, feeding disorder, hyponatremia, lactic acidosis;
***Neoplasms benign, malignant and unspecified*:** Ewing's sarcoma;

***Nervous system disorders*:** brain injury, brain oedema, coma, convulsion, encephalopathy, epilepsy, headache, intracranial pressure increased, lethargy, meningeal disorder, motor developmental delay, nervous system disorder;

***Respiratory*:** respiratory failure, respiratory arrest;

***Vascular disorders*:** vasoplegia syndrome.

DRUG INTERACTIONS

Overview
No clinical drug interaction studies have been performed with Carbaglu.

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.

Drug-Drug Interactions
Administration of agents that may cause hyperammonia through pharmacodynamic interactions include valproate, carbamazepine, phenobarbital, topiramate, corticosteroids and haloperidol. Caution is recommended when-these agents are co-administered with Carbaglu.

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions
Effects of Carbaglu on the ability to drive and use machines are not known.

DOSAGE AND ADMINISTRATION

Dosing Considerations
Based on clinical experience, the treatment may be started as early as the first day of life.

Recommended Dose and Dosage Adjustment
The initial dose should be 100 mg/kg/day, up to 250 mg/kg/day if necessary. Concomitant administration of other ammonia lowering therapies is recommended.

The recommended maintenance dose should be titrated to target normal plasma ammonia level for age. It should be adjusted individually (see WARNINGS AND PRECAUTIONS) based on individual plasma ammonia levels and clinical symptoms.
In the long term, it may not be necessary to increase the dose according to body weight as long as adequate metabolic control is achieved; doses range from 10 mg/kg/day to 100 mg/kg/day.
Carbaglu responsiveness test: It is recommended to test individual responsiveness to Carbaglu before initiating any long term treatment. For example:

- In a comatose child, start with a dose of 100 to 250 mg/kg/day and measure ammonia plasma concentration at least before each administration; it should normalise within a few hours after starting Carbaglu.
- In a patient with moderate hyperammonemia, administer a test dose of 100 to 200 mg/kg/day for 3 days with a constant protein intake and perform repeated determinations of ammonia plasma concentration (before and 1 hour after a meal); adjust the dose in order to maintain normal ammonia plasma levels.

Missed Dose
In the event a dose is missed, the dose should not be doubled to make up for the forgotten doses. The next dose should be taken according to the regular dosing interval.

Administration

Oral administration: Carbaglu tablets should not be swallowed whole or crushed.
Based on pharmacokinetic data and clinical experience, it is recommended to divide the total daily dose into two to four doses to be given before meals or feedings. The breaking of the tablets in halves allows most of the required posology adjustments. Occasionally, the use of quarter tablets may also be useful to adjust the posology prescribed by the physician.
Each 200 mg tablet should be dispersed in a minimum of 2.5 ml of water and ingested immediately. Use in other foods or liquids has not been studied clinically and therefore is not recommended.

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.

The suspension has a slightly acidic taste.

Nasogastric administration: It is recommended to divide the total daily dose into two to four doses to be given before feedings. For patients who have a nasogastric tube in place, Carbaglu should be administered as follows:

Adults

- 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.

Pediatrics

- 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 the nasogastric tube. Discard the unused portion;
- Flush with additional water to clear the nasogastric tube.

OVERDOSAGE

One patient treated with a dose increased up to 650 mg/kg/day of carglumic acid developed symptoms of intoxication characterized as a sympathomimetic reaction: tachycardia, profuse sweating, increased bronchial secretion, increased body temperature and restlessness. These symptoms resolved upon reduction of the dose.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Carglumic acid is a synthetic structural analogue of N-acetylglutamate (NAG), which is the essential allosteric activator of carbamoyl phosphate synthetase 1 (CPS1) in liver mitochondria. CPS 1 is the first enzyme of the urea cycle, which converts ammonia into urea. NAG is the product of NAGS, a mitochondrial enzyme. Carglumic acid acts as replacement for NAG in NAGS deficiency patients by activating CPS 1.

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 was identified.

Pharmacokinetics

The pharmacokinetics of carglumic acid has been studied in healthy male volunteers using carglumic acid dispersible tablets at 100 mg/kg.

Table 2 - Summary of Carbaglu's Pharmacokinetic Parameters in a Healthy Male Volunteers

	C_{max}	$t_{½}$ (h)	$AUC_{0\text{-}inf}$	Clearance	Volume of distribution
Mean	2.7 µg/ml	6 h	22.56 µg/ml/h	5.78L/min	2783 L
S.D.	± 0.8	± 2	± 7.02	± 1.74	± 1107
Range	1.8-4.8	3-10	12.44-38.43	2.96-9.70	1616-5797

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

Distribution: The apparent volume of distribution was 2783 L (range: 1616-5797). Diffusion into erythrocytes is non-existent. Protein binding has not been determined.

Metabolism: A proportion of carglumic acid may be metabolized by the intestinal bacterial flora. Glutamic acid in feces and metabolites with a peak at 36-48 hours and a very slow decline (half-life approximately 100 hours) were identified in plasma.

The likely end product of carglumic acid metabolism is carbon dioxide, which is eliminated through the lungs.

Excretion: Following administration of a single radiolabeled oral dose of 100 mg/kg of body weight, 9% of the dose is excreted unchanged in the urine and up to 60% in the feces. The apparent total clearance of Carbaglu was 5.78 L/min (range: 2.96-9.70) and the renal clearance was 295 mL/min (range 204-445).

The plasma elimination curve of carglumic acid is biphasic with a rapid phase over the first 12 hours after administration followed by a slow phase (terminal half-life up to 28 hours).

Special Populations and Conditions

Pediatrics (≤ 18 years of age): There are no apparent differences in clinical response between adults and pediatric NAGS deficiency patients treated with Carbaglu.

Geriatrics (≥ 65 years of age): Carbaglu has not been studied in the geriatric population. Therefore, the safety and effectiveness in geriatric patients have not been established.

Hepatic Insufficiency: The pharmacokinetics of Carbaglu has not been evaluated in hepatic impaired patients.

Renal Insufficiency: The pharmacokinetics of Carbaglu has not been evaluated in renal impaired patients.

Gender, Race and Genetic polymorphism: Influence of gender, age and genetic polymorphisms on the pharmacokinetics of Carbaglu have not been evaluated.

STORAGE AND STABILITY

Store under refrigeration (2 - 8°C).

After first opening of the tablet container:

- Keep the container tightly closed in order to protect from moisture.
- Discard one month after first opening.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Carbaglu is a white and elongated dispersible tablet with three score marks and engraved "C" on one side. The tablet can be divided into equal portions.

Each tablet contains 200 mg of carglumic acid.

Nonmedicinal ingredients are as follow: croscarmellose sodium, hypromellose, microcrystalline cellulose, silica colloidal anhydrous, sodium laurilsulfate, sodium stearyl fumarate.

Carbaglu is available as 5 and 60 tablets in a polypropylene bottle with a polyethylene cap and desiccant unit.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

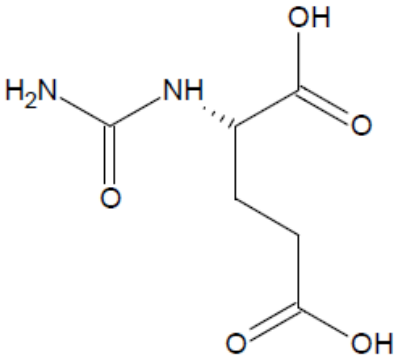
Drug Substance

Proper name: Carglumic acid

Chemical name: N-carbamoyl-L-glutamic acid or (2S)-2-(carbamoylamino) pentanedioic acid

Molecular formula and molecular mass: $C_6H_{10}N_2O_5$
190.16

Structural formula:



Physicochemical properties: Carglumic acid is a white crystalline powder which is soluble in boiling water, slightly soluble in cold water, and practically insoluble in organic solvents such as cyclohexane, dichloromethane and ether.The pH of a 0.5% aqueous solution is between 2.2 and 3.2 and its melting point is 159°C to 163°C. pKa values of 2.50, 3.55, 8.60 have been determined for carglumic acid.

CLINICAL TRIALS

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 3.

Table 3: Baseline Characteristics of 23 NAGS deficiency Patients treated with Carbaglu in a Retrospective Case Series

		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 4 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 4: 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.

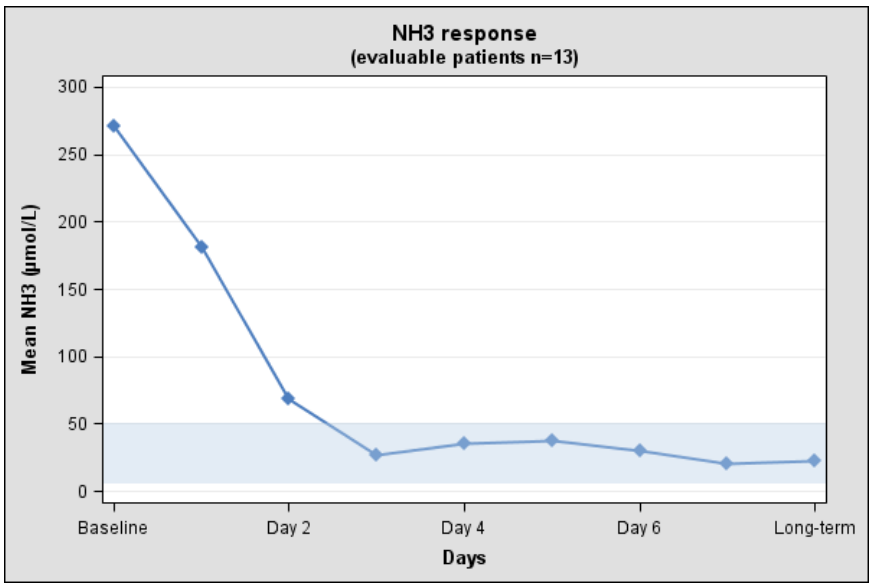


Figure 1: Ammonia response for 13 evaluable NAGS deficiency patients at baseline and after treatment with Carbaglu

DETAILED PHARMACOLOGY

Pharmacodynamics

Carglumic acid is an amino acid and a structural analogue of NAG. NAGS, a mitochondrial enzyme, catalyzes the formation of NAG, an essential, allosteric activator of CPS1, the first enzyme of the urea cycle. Carglumic acid acts as a replacement for NAG in NAGS deficiency patients by activating CPS1.

In patients with NAG deficiency, carglumic acid was shown to induce a rapid normalisation of plasma ammonia levels, usually within 24 hours. When the treatment was instituted before any permanent brain damage, patients exhibited normal growth and psychomotor development.

Other studies have been conducted in rats under different experimental conditions leading to increased ammonia availability (starvation, protein-free or high-protein diet). Carglumic acid was shown to decrease blood ammonia levels and increase urea levels in blood and urine, whereas the liver content of carbamoyl phosphate synthetase activators was significantly increased.

Safety Pharmacology

Carglumic acid administered orally in rats at doses up to 1000 mg/kg had no statistically significant effect on central nervous system and respiratory functions.

In isolated canine Purkinje fibers, carglumic acid had no statistically significant effect on action potential at concentrations up to19 µg/ml. There were also no changes in blood pressure, heart rate and cardiac conduction times (ECG) including QT interval and QTc in conscious dogs after oral administration of up to 1000 mg/kg carglumic acid.

TOXICOLOGY

Acute Toxicity
Single doses of carglumic acid up to 2800 mg/kg orally and 239 mg/kg intravenously did not induce any mortality or abnormal clinical signs in adult rats.

Subchronic and Chronic Toxicity
In a 2-week repeat-dose toxicity study in newborn rats, carglumic acid was administered orally from day 4 to day 21 post-partum at 250, 500, 1000 and 2000 mg/kg/day. The high dose of 2000 mg/kg/day induced the death of all pups; no cause of death was identified. At 1000 mg/kg/day, orange colored feces, a slight reduction of body weight gain, decreased thymus weight, and dilated kidney pelvis were observed. The non-observed-adverse-effect level (NOAEL) was 500 mg/kg/day (approximately 7.5 times human exposure at the maximum recommended human dose (MRHD) of 250 mg/kg, based on AUC comparisons).

In a 26-week repeat-dose toxicity study, carglumic acid was administered orally to young rats (4 weeks old at the start of the treatment) at 500 and 1000 mg/kg/day. There was no treatment-related effect on teeth, body length, ophthalmoscopy, and bone mineral density. Increased incidences of histopathological findings in the harderian gland (necrotizing inflammation), kidney (pelvis and tubular dilatation), and liver (multifocal coagulative hepatocellular necrosis) were observed at 1000 mg/kg/day. In addition, ptyalism (excess salivation), a slight reduction in body weight gain, decreased urine pH, and elevated liver weights were seen at this dose level (1000 mg/kg/day). The NOAEL for general toxicity was 500 mg/kg/day (approximately 10 times MRHD based on AUC). In this study, carglumic acid did not induce immunotoxicity up to 1000 mg/kg/day (up to approximately 14 times MRHD based on AUC).

Genotoxicity
Carbaglu showed no significant mutagenic activity in a battery of genotoxicity studies performed in vitro and in vivo.

Carcinogenicity
Carcinogenicity studies were not performed with Carbaglu.

Reproduction and Development
In the 26-week repeat-dose study in young rats, treated males were mated with additional untreated virgin females from week 26. No adverse effects on mating and fertility were observed at oral doses up to 1000 mg/kg/day (up to approximately 14 times MRHD based on AUC).

In a combined fertility and embryo-fetal development study, female rats were orally administered 500 or 2000 mg/kg/day carglumic acid 15 days prior to mating through gestation day 17. No adverse effects on mating, fertility, and embryo-fetal development were observed at the doses tested, although signs of maternal toxicity occurred at the high dose of 2000 mg/kg/day. The NOAEL for female fertility and embryo-fetal development in rats was 2000 mg/kg/day (approximately 28 times MRHD based on AUC). The NOAEL for maternal toxicity in rats was 500 mg/kg/day (approximately 9 times MRHD based on AUC).

Carglumic acid administered to pregnant rabbits during organogenesis was not embryo-fetal toxic or teratogenic at oral doses of 500 and 1000 mg/kg/day. Maternal toxicity occurred at the high dose of 1000 mg/kg/day. The NOAEL for embryo-fetal development in rabbits was 1000 mg/kg/day (approximately 2.4 times MRHD based on AUC). The NOAEL for maternal toxicity in rabbits was 250 mg/kg/day (approximately 1.4 times MRHD based on AUC).

In a pre- and postnatal developmental toxicity study in rats, carglumic acid was administered to F0 female rats from implantation up to weaning of the progeny at oral doses of 500 and 2000 mg/kg/day. Carglumic acid was secreted in the milk of lactating rats. Reduced pup survival during the first four postnatal days was observed at 2000 mg/kg/day and reductions in offspring body weight/body weight gains were observed at 500 and 2000 mg/kg/day. Maternal toxicity was observed at both dose levels in F0 females. The maternal systemic exposures after 500 and 2000 mg/kg/day were ten times and twenty four times the clinical exposure at MRHD, based on C_{max}.

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PART III: CONSUMER INFORMATION

Carbaglu®
Carglumic acid dispersible tablets

This leaflet is part III of a three-part "Product Monograph" published when Carbaglu was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Carbaglu. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Use Carbaglu if you are missing a liver enzyme called N-acetylglutamate synthase (NAGS):

- To treat high ammonia in the blood. It may be used with other therapies as discussed with your doctor. This includes a low protein diet
- To maintain your blood ammonia at a normal level

What it does:
Patients with NAGS deficiency lack a liver enzyme. It normally helps break down ammonia that builds up in the blood after eating protein. This is toxic to the body and especially to the brain. Carbaglu activates an enzyme that breaks down ammonia. It reduces blood ammonia levels and its toxic effects.

When it should not be used:
Do not take Carbaglu if you are:

- allergic to this drug or to any of its ingredients

Do not breastfeed while taking Carbaglu.

What the medicinal ingredient is:
Carglumic acid.

What the nonmedicinal ingredients are:
Croscarmellose sodium, hypromellose, microcrystalline cellulose, silica colloidal anhydrous, sodium laurilsulfate, sodium stearyl fumarate.

What dosage forms it comes in:
Dispersible tablet, 200 mg.

The tablet can be divided into equal portions.

WARNINGS AND PRECAUTIONS

Episodes of high ammonia blood level with rapid start should be treated immediately. Ammonia is toxic especially to the brain. It can lead to reduced consciousness and coma.

Treatment should be started under care of a doctor specialized in your condition. Dose will be adjusted by your doctor to keep your ammonia blood levels normal.

During episodes of high ammonia blood levels, your doctor will tell you what to do. He may tell you to increase your calories and not to eat protein for 1 or 2 days. When your ammonia level is back to normal, your doctor will tell you if you can eat protein again. You may have to take arginine supplements or restrict your protein intake.

Your doctor will examine your liver, kidney, heart, and blood regularly. He will make sure Carbaglu is helping you and not causing harmful effects.

If you are pregnant and taking Carbaglu, consult your doctor.

INTERACTIONS WITH THIS MEDICATION

Carbaglu can react with other drugs. Tell your doctor about all the drugs you take. Include those prescribed by other doctors. Report your use of vitamins, minerals, natural or alternative medicines.

The following may interact with Carbaglu by raising the blood ammonia levels:

- Drugs that treat epilepsy. These include valproate, carbamazepine, phenobarbital and topiramate
- Corticosteroids
- Haloperidol

PROPER USE OF THIS MEDICATION

Take Carbaglu before meals or feedings. Do NOT crush or swallow Carbaglu whole.

Always mix Carbaglu in a minimum of 2.5 ml of water. Carbaglu tablets do not dissolve completely in water. Part of the tablet may stay in the mixing container.

By Mouth:

- swallow Carbaglu immediately once you mix it with water
- rinse the container with more water
- swallow this extra water immediately as part of your dose

By Nasogastric Tube:

- give Carbaglu immediately once you mix it with water
- give it by fast push through a syringe
- flush with additional water to clear the nasogastric tube.

The mixture has a slightly acidic taste.

Usual Dose:
Your doctor will determine the dose based on your weight and the level of ammonia in your blood. Do not change your dose without checking with your doctor or pharmacist.

Divide the total daily amount of Carbaglu into two to four doses as prescribed by your doctor.

Usual Initial Daily Dose: 100 mg/kg/day, up to 250 mg/kg/day if necessary.

Daily Maintenance Dose: is individualized for each patient. It ranges from 10 mg/kg/day to 100 mg/kg/day.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Do not wait for any signs or symptoms to appear before seeking medical attention, as they may not occur immediately.

In a case of overdose, the following symptoms were observed: rapid heartbeat, heavy sweating, coughing up mucous, fever and feeling restless. These symptoms stopped when the dose was decreased.

Missed Dose:
Do not take a double dose to make up for forgotten individual doses. If you have forgotten a dose, continue to take the next dose at the regularly scheduled time.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effects associated with Carbaglu are:

- stomach pain, diarrhea
- fever, infections, ear infection, nose and throat infections, inflammation of the tonsils
- anemia
- headache

Carbaglu can cause some serious side effects such as pneumonia, drowsiness and vomiting.

It can also cause some serious side effects such as pneumonia, drowsiness, and vomiting.

Some of these side effects may be temporary. Others may be serious or dose-related. Consult your doctor if you experience these or any other side effects.

Carbaglu can cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results.

This is not a complete list of side effects. For any unexpected effects while taking Carbaglu, contact your doctor or pharmacist.

HOW TO STORE IT

Keep out of the reach of children.

Keep Carbaglu in the fridge (2 - 8°C).

After first opening the tablet container:

- Keep the container tightly closed in order to protect from moisture.
- Discard one month after first opening.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals, can be found by contacting Médunik Canada at:
950 Michèle-Bohec Blvd.
Blainville, Quebec, Canada
J7C 5E2
Tel: 1-855-633-8645
Fax: 1-888-588-8508
www.medunikcanada.com

This leaflet was prepared by Médunik Canada for Orphan Europe S.A.R.L.

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