Carbaglu® (carglumic acid)
Monograph

Carbaglu® carglumic acid

INDICATION AND IMPORTANT SAFETY INFORMATION

Indications and Usage

Carbaglu® (carglumic acid) is a Carbamoyl Phosphate Synthetase 1 (CPS 1) 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 are recommended.
- 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.

Important Safety Information

HYPERAMMONEMIA :

- Management of hyperammonemia due to N-acetylglutamate synthase (NAGS) deficiency and CARBAGLU treatment should be initiated by a physician experienced in the treatment of metabolic disorders.
- 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.
- 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.

THERAPEUTIC MONITORING:

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

NUTRITIONAL MANAGEMENT:

- 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.

The most common adverse reactions in ≥ 13% of patients are: infections, vomiting, abdominal pain, pyrexia, tonsillitis, anemia, ear infection, diarrhea, nasopharyngitis, 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.

No drug interaction studies have been performed with CARBAGLU. There is no human pregnancy data, but decreased survival and growth occurred in animal offspring.

Breast feeding by a mother taking CARBAGLU is not recommended.

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

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ABBREVIATIONS

AE	Adverse event
API	Active pharmaceutical ingredient
ARG	Arginase
ASL	Argininosuccinate lyase
ASS	Argininosuccinate synthetase
Cmax	Maximum plasma concentration
CNS	Central nervous system
CPS1	Carbamoyl phosphate synthetase 1
DNA	Deoxyribonucleic acid
GLN	Glutamine
GLU	Glutamate
GMP	Good Manufacturing Practices
GS	Glutamine synthetase
HPA	Hydantoin-5-propionic acid
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation
INN	International Non Proprietary Name
IR	Infrared
LC/MS-MS	Liquid chromatographic-tandem mass spectrometry
NAG	N-acetylglutamate
NAGS	N-acetylglutamate synthase
NOAEL	No observable adverse effect level
NOEL	No observable effect level
OTC	Ornithine transcarbamylase
PK	Pharmacokinetic
RH	Relative humidity
SAE	Serious adverse event
Tmax	Time to reach maximum plasma concentration
UCD	Urea cycle disorders
UV	Ultraviolet
WHO	World Health Organization

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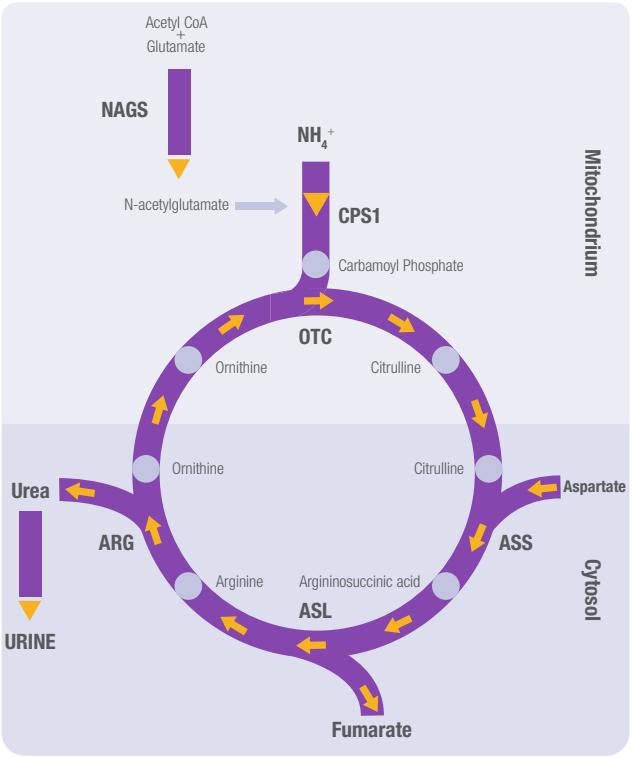
1.0 THE UREA CYCLE AND UREA CYCLE DISORDER

The urea cycle is the primary pathway for waste of nitrogen excretion in humans. Approximately 80% of excreted nitrogen is in the form of urea, which is produced primarily in the liver (Burton 2000).



As presented in the diagram, the urea cycle is comprised of the following:

- 5 catalytic enzymes - carbamoyl phosphate synthetase 1 (CPS1), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL) and arginase (ARG)
- A cofactor-producer enzyme: N-acetylglutamate synthase (NAGS)
- Two transporters - ornithine translocase (ORNT1) and citrin (Ah Mew et al 2015)

Although these enzymes are found in other tissues, the urea cycle occurs solely in the liver, and this organ consequently acts as the main ammonia detoxification center (Walser 1983).

The NAGS, CPS1, and OTC enzymes are found within the mitochondria. The mitochondrial part of the urea cycle transforms an initial ammonia molecule into a molecule of citrulline. Citrulline then enters the cytosol where it binds a second ammonia molecule carried by aspartate before ultimate transformation to urea. This cytosolic part of the cycle is catalyzed by the ASS, ASL, and ARG enzymes. The final product of the urea cycle is de novo synthesis of arginine, which is a non-essential amino acid.

Enzymes of the Urea Cycle:
NAGS: **N-acetylglutamate synthase**
CPS1: **carbamoyl phosphate synthetase 1**
OTC: **ornithine transcarbamylase**
ASS: **argininosuccinate synthetase**
ASL: **argininosuccinate lyase**
ARG: **arginase**

The activity of the urea cycle does not depend solely upon these 6 enzymes; it is also regulated by other enzyme systems, such as mitochondrial membrane transport systems, which allow aspartate-glutamate and citrulline-ornithine exchange (Summar 2001, Summar 2005a, Tuchman 2002).

Urea cycle disorders (UCD) are inherited metabolic disorders resulting from defects in the metabolism of the extra nitrogen from the breakdown of protein and other nitrogen-containing molecules.

Severe deficiency or total absence of activity of the cofactor-producing enzyme (NAGS) or any of the first four urea cycle enzymes (CPS1, OTC, ASS, ASL) results in the accumulation of ammonia and other precursor metabolites during the first few days of life (Ah Mew et al 2015). Ammonia is a toxic product of protein catabolism. UCD can present with extreme variability depending on residual urea cycle activity in the liver, and clinical presentation can be seen in all age groups (Summar 2001). The significant morbidity and mortality of these disorders arise from acute and chronic neurotoxicity associated with massive hyperammonemia (Bachmann 2005). The symptoms may range from life-threatening episodes of hyperammonemia in the newborn period (neonatal/early onset) to gastrointestinal disturbances, neurological symptoms such as recurrent headaches and drowsiness, and psychiatric disturbances including behavioral changes and hallucinations, from age one month into adulthood (late onset) (Kleppe 2003, Summar 2001). The incidence for the United States is predicted to be 1 UCD patient for every 35,000 births presenting about 113 new patients per year across all age groups (Summar 2013).

2.0 NAGS DEFICIENCY

NAGS deficiency is the rarest of the UCDs (Caldovic 2010, Tuchman 2008). NAGS deficiency is an inherited, autosomal recessive metabolic disorder (Caldovic 2002, Caldovic 2003, Caldovic 2005).

NAGS is a mitochondrial liver enzyme that is essential for the urea cycle (Roth 2006). NAGS catalyzes the formation of N-acetylglutamate (NAG) from glutamate and acetyl-CoA, which then NAG acts as an allosteric activator of CPS1, the first enzyme of the urea cycle (Cartegena 2013). If NAGS is defective, NAG synthesis is impaired and there is no activation of CPS1 to trigger the urea cycle. The activity of the urea cycle is regulated by the rate of synthesis of NAG.

The impairment of ammonia detoxification due to NAGS deficiency results in acute and chronic hyperammonemia, hyperglutaminemia and, eventually, hypocitrullinemia.

Hyperammonemia and hyperglutaminemia are particularly toxic to the central nervous system (CNS) (Albrecht 1998, Broere 2000).

NAGS deficiency represents a serious, life-threatening clinical condition (Caldovic 2002, Guffon 1995, Schubiger 1991). In published cases, NAGS deficiency has presented at ages ranging from the neonatal period to the fifth decade of life (Ah Mew 2011).

Patients with complete NAGS deficiency present with acute severe hyperammonemia within the first few days of life (Caldovic 2005, Nordenström 2007). The clinical course in the neonatal period may be lethal. Left untreated or insufficiently corrected, this condition leads to cerebral edema, coma, and eventually death. For those children who survive, psychomotor retardation is a frequent outcome (Schubiger 1991). Patients with partial NAGS deficiency (late onset) can present symptoms at almost any time of life due to any stressful event such as an infection, trauma, vaccination (Kingsley 2006), surgery, pregnancy, etc.

2.1 HEREDITY

NAGS deficiency is transmitted as an autosomal recessive trait and consequently affects boys and girls to the same extent in both the neonatal onset and late onset forms. Heterozygous individuals are clinically asymptomatic (Caldovic 2005, Caldovic 2007).

The gene coding for NAGS has been identified and is located on chromosome 17 (Caldovic 2002, Elpeleg 2002).

2.2 INCIDENCE

NAGS deficiency is the rarest of the UCD (Caldovic 2010, Tuchman 2008).The true incidence is not known, although it is suspected to be < 1 in 2 million births (Summar 2013). The incidence for the United States is predicted to be 1 urea cycle disorder patient for every 35,000 births presenting about 113 new patients per year across all age groups (Summar 2013).

2.3 PATHOPHYSIOLOGY

In NAGS deficiency, the lack of adequate NAG results in failure to activate the enzyme CPS1. Signs and symptoms occur when ammonia fails to fix into carbamoyl phosphate effectively, thus disabling the urea cycle. This leads to accumulation of:

a) ammonia;
b) glutamine (Gln) and eventually alanine;
c) transamination products of pyruvate and glutamate (Glu).

The major cause of mortality and morbidity in many UCD, including NAGS deficiency, is hyperammonemia (Jouvet 2007). Most therapeutic interventions have focused on prevention and treatment of hyperammonemia. However, as a cohort of treated patients gets older, other complications have appeared even without a significant history of recurrent hyperammonemia (Bachmann 2005, Cederbaum 2001, Gomceli 2007, Nagata 1991, Smith 2005).

Most pathophysiologic studies to date have focused on the mechanisms of ammonia neurotoxicity (Brusilow 1995, Gropman 2004, Herndon 2003). However, the specific mechanisms are still controversial and diverse. The brain, like the other extrahepatic organs, lacks a complete urea cycle. Hence, the brain relies on Gln synthesis for the removal of excess ammonia and the temporary storage of nitrogen. As this process is predominantly localized in the astrocytes, acute hyperammonemia causes increased intracellular production of Gln from Glu and ammonia via glutamine synthetase (GS), which leads to astrocyte swelling and dysfunction. Excess Gln is released into the extracellular space, and directly alters the local astrocyte-neuronal synaptic environment (Felipo 1994). A consequent imbalance of excitatory versus inhibitory neurotransmission occurs because of increased Glu production in conjunction with decreased synaptic uptake of Glu. Over time, chronic hyperammonemia causes changes reminiscent of Alzheimer type II astrocytosis (Robinson 1995).

Acute hyperammonemia also alters astrocyte protein expression (Jackson 1986), including changes in GS, glial fibrillary acidic protein, Glu transporter, nitric oxide synthase, and peripheral-type benzodiazepine receptors. All of these changes can result in alterations in the brain's ability to remove additional ammonia, to regulate cerebral blood flow, and to maintain energy homeostasis and neurotransmission.

2.4 NEONATAL/EARLY ONSET FORMS

Approximately half of all reported cases of NAGS deficiency had onset of clinical symptoms in the neonatal period (Caldovic 2010). The clinical presentation of the disease is described below (Bachman 1988, Gessler 2010, Guffon 1995, Nordenström 2007, Roth 2006, Ah Mew 2011):

NAGSD Neonatal/Early Onset Clinical Presentation	
Infants delivered at term are usually relatively healthy and well	There is a symptom-free interval of several hours to several days prior to onset of the first symptoms; this period represents the time for ammonia to accumulate in the body.
Initial symptoms include: poor feeding vomiting gradual lethargy muscular hypotonia hypothermia polypnea resulting in respiratory alkalosis (This is highly characteristic of hyperammonemic encephalopathy).	Subsequently, there is a rapidly progressive neurological distress that is fatal if untreated; symptoms include: hypotonic coma convulsions apnea requiring assisted ventilation signs of cerebral edema on brain imaging.

2.5 LATE ONSET FORMS

The clinical picture and development of the late onset forms vary widely: they may occur in the first months of life or in adulthood. Clinical symptoms result primarily from hyperammonemia, and the most common clinical findings include central nervous system symptoms, such as lethargy, irritability or somnolence. In general, patients with late onset forms can present with (Bélanger-Quintana 2003, Caldovic 2005, Elpeleg 1989, Cartagena 2013):

NAGSD Late Onset Clinical Presentation		
Gastrointestinal presentations (possibly accompanied by hepatic involvement): chronic or paroxysmal vomiting anorexia with refusal to eat high-protein foods, generally resulting in delayed physical growth abdominal pain hepatomegaly recurrent episodes of cytolysis	Neurological presentations with psychomotor retardation involving either chronic encephalopathy with epileptic seizures or episodes of headache or drowsiness and neurological accidents that may even comprise inaugural hyperammonemic coma	Psychiatric presentations include behavioral changes, hallucinations

Acute decompensation episodes are often triggered by an increase in protein intake following a change in dietary habit or have been precipitated by illness, pregnancy, or surgery (Elpeleg 1989, Kingsley 2006, Summar 2005a, Ah Mew 2011).

The prognosis for these forms varies according to age at onset, whether or not neurological impairment is present at the time of diagnosis, and whether any subsequent episodes of decompensation occur.

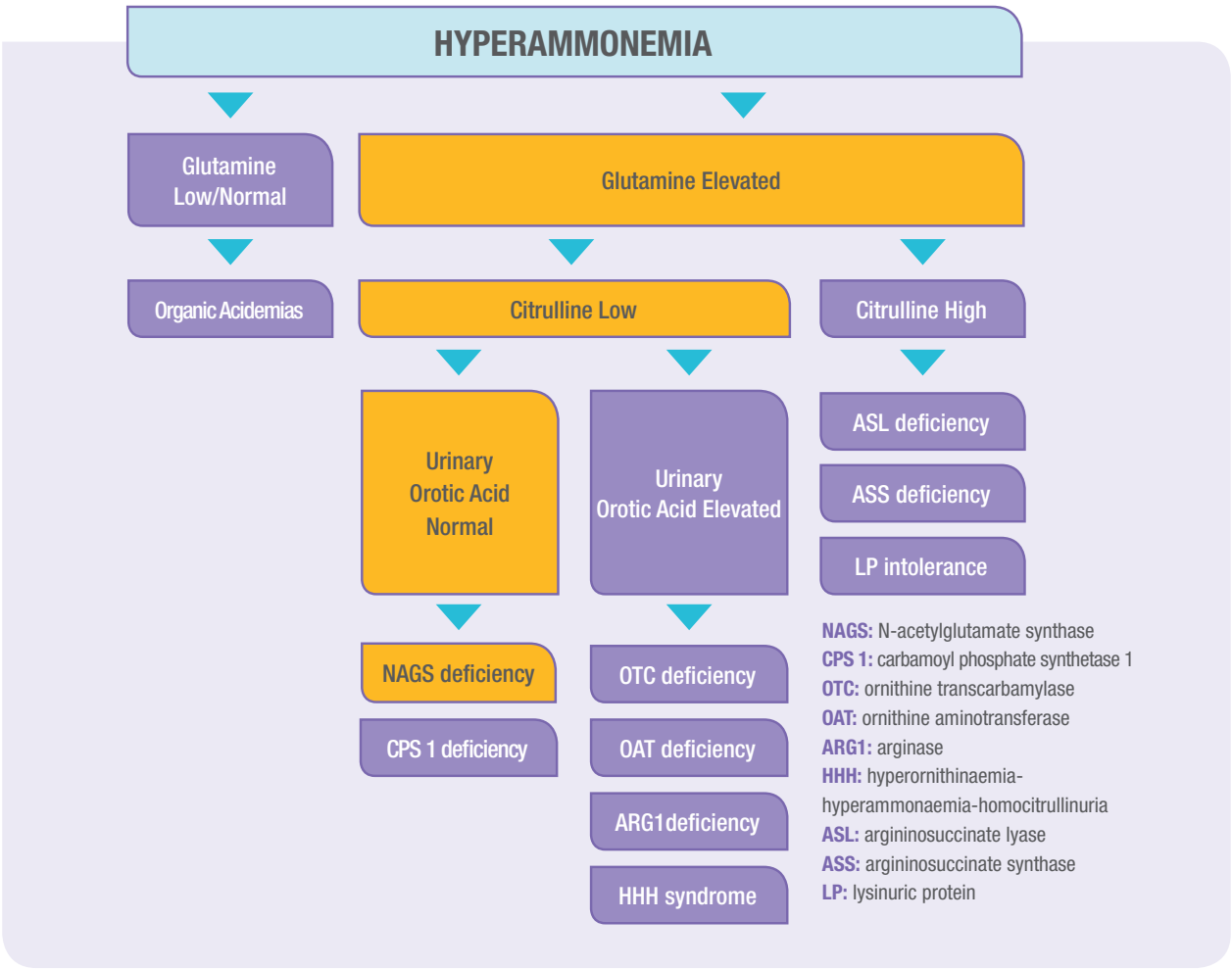
2.6 DIAGNOSIS

In order to diagnose NAGS deficiency, the first step is to suspect urea cycle disorders.

2.6.1 DIAGNOSIS OF UCD

There are general and specific signs and symptoms of UCD, including unexplained coma or encephalopathy associated with catabolic stress (newborn period, infectious illness, and postpartum), and nonspecific neurologic or gastrointestinal symptoms especially associated with increased protein intake (Kleppe 2003). A wide spectrum of clinical presentations has been reported in the literature. The symptoms may range from life-threatening episodes of hyperammonemia in the newborn period (early onset) to gastrointestinal disturbances, neurological symptoms such as recurrent headaches and drowsiness, and psychiatric disturbances including behavioral changes and hallucinations, in adulthood (Summar 2001).

The diagnosis of a urea cycle disorder is based on clinical suspicion and biochemical and molecular genetic testing. A plasma ammonia concentration of 150 µmol/L or higher associated with a normal anion gap and a normal plasma glucose concentration is an indication for the presence of a UCD. Plasma quantitative amino acid analysis and measurement of urinary orotic acid can distinguish between the specific UCDs. A definitive diagnosis of a urea cycle defect depends on either molecular genetic testing or measurement of enzyme activity. Molecular genetic testing is possible for all urea cycle defects (Ah Mew et al 2015).



Adapted from Häberle J, et al. (2012) Suggested guidelines for the diagnosis and management of urea cycle disorders. Orphanet J Rare Dis ;7:32.

A summary of urea cycle enzyme deficiencies for each of the UCDs is provided below (Kleppe 2003, Summar 2005b).

Summary of Urea Cycle Enzyme Deficiencies

Enzyme deficiencies	Heredity	Biochemical profile	Clinical features
NAGS	Autosomal recessive, chromosome 17q	↑glutamine-alanine, ↓citrulline-arginine, urinary orotic acid normal or low	• Very rare • Severe hyperammonemia
CPS1	Autosomal recessive, chromosome 2q	↑glutamine-alanine, ↓citrulline-arginine, urinary orotic acid normal or low	• Rare • Severe hyperammonemia
OTC	Recessive, X-linked (Xp21)	↑glutamine-alanine, ↓citrulline-arginine, ↑↑orotic acid	• Most common type • Girls: carriers or symptomatic (lyonisation) • Boys: very severe neonatal or late onset forms (residual activity)
ASS (citrullinemia)	Autosomal recessive, chromosome 9q	↑glutamine-alanine, ↑↑↑citrulline, ↓arginine, ↑orotic acid	• Severe hyperammonemia
ASL (argininosuccinic aciduria)	Autosomal recessive, chromosome 7q	↑glutamine-alanine, ↑↑↑argininosuccinic acid (plasma + urine) ↑↑citrulline, ↓↓↓arginine, ↑orotic acid	• Less severe hyperammonemia • Mental retardation of gradual onset (neurotoxicity of argininosuccinic acid) • Very severe hepatomegaly • Hair shaft anomaly (trichorrhexis nodosa)
Arginase	Autosomal recessive, chromosome 6q	↑↑↑arginine, ↑orotic acid	• Very rare • Hyperammonemia less frequent • Progressive spastic diplegia • Mental retardation

2.6.2 DIAGNOSIS OF NAGS DEFICIENCY

Depending on the age at NAGS deficiency onset , some or all of the following symptoms can clinically manifest in patients (Endo 2004, Gomceli 2007, Kleppe 2003, Scaglia 2004a): anorexia, irritability, heavy or rapid breathing, lethargy, vomiting, disorientation, somnolence, combativeness, and hypotonia. Coma and fatal cerebral edema will be the outcome if an effective treatment is not implemented rapidly.

Diagnosis of NAGS deficiency is made based on the following assessments (Bachmann 1982, Bachmann 2003a, Bachmann 2003b, Barsotti 2001, Colombo 1995, Huizenga 1994, Saudubray 2007, Steiner 2001):

- **Blood ammonia levels:** the neonatal onset forms of NAGS deficiency have extremely high blood ammonia levels. Affected newborns may experience ammonia levels from>150 µmol/L up to or possibly exceeding 1000 µmol/L (normal concentration in newborns: <100 µmol/L). In the late onset forms, although blood ammonia levels are always high during the acute phase, they may be normal at other times (the normal range varies between laboratories but is generally <50 µmol/L). Thus, total nitrogen testing must be performed carefully.
- **Amino acids:** plasma levels of Gln are elevated. Urinary amino acids are non-diagnostic in NAGS deficiency but may be important in order to help rule out hyperammonemia-hyperornithinemia-homocitrullinuria or lysinuric protein intolerance.
- **Urinary orotic acid:** level is within normal range or low.
- **Urinary organic acids:** are within reference ranges in NAGS deficiency. It is essential to rule out organic acid disorders, which can present with similar signs and symptoms including hyperammonemia.
- **Liver biopsy:** might be helpful if performed under protein load procedure but the results are not always conclusive; basal enzyme activity may not always be pathognomonic (Colombo 1982, Heckmann 2005, Jackson 1986). The invasive nature of a liver biopsy limits its current use.
- **DNA testing:** final confirmation comes through molecular diagnosis with the specific DNA genotype (mutation). This has been available since 2003.

After evaluation of symptoms and biochemical parameters, the initial diagnosis of NAGS deficiency can be supported by liver biopsy, but the results are not always conclusive. The DNA mutation analysis is now used to confirm diagnosis. Approximately 20 causative mutations have been reported worldwide for NAGS deficiency (Caldovic 2007, Haberle 2003).

Detection of a mutation in the NAGS gene, mapped to chromosome 17q21.31, confirms the diagnosis of NAGS deficiency allowing specific therapy, detection of carriers, and prenatal diagnosis (Caldovic 2002, Caldovic 2003, Caldovic 2005, Caldovic 2007, Häberle 2003, Häberle 2004, Morizono 2004). However, molecular genetic testing results are usually available within few weeks, thus genetic testing is considered a confirmatory diagnostic tool. Treatment of acute hyperammonemia should not be delayed if NAGS deficiency is suspected.

Until final confirmation is available from the DNA testing or hepatic enzymatic assay, a diagnosis can usually be narrowed down to either NAGS deficiency or CPS1 deficiency. Both of these diseases have similar clinical and biochemical findings including hyperammonemia, elevated Gln levels, no specific increase of urea cycle intermediates, and normal orotic aciduria, with exclusion of organic aciduria (Bachmann 1982, Caldovic 2002, Caldovic 2010).

2.7 TREATMENT OF NAGS DEFICIENCY

Since the prognosis is strongly influenced by coma and peak ammonia levels, once a diagnosis of a UCD is made, treatment should be tailored to the specific urea cycle disorder (Haberle,et al 2012, Summar, Tuchman 2001). Patients in hyperammonemic crisis should be transferred to a specialist center (Haberle, et al 2012).

The primary goal is to rapidly return plasma ammonia concentration to normal physiologic levels, prevent recurrent hyperammonemia and to avoid the associated complications of the CNS (Valayannopoulos 2005). Early prompt diagnosis of hyperammonemia is crucial for a better outcome. The start of ammonia detoxification and reversing catabolism must not be delayed (Haberle, et al 2012). Long-term secondary goals include maintenance of optimal growth and neurological development by avoiding nutrient imbalance and insufficiency and amino acid deficiencies. In the acute phase of severe hyperammonemia, the best way to reduce plasma ammonia concentration quickly is by dialysis. Other methods are hemofiltration and hemodialysis and protein restriction diet (Ah Mew et al 2015).

Treatment of Acute Manifestations

- **Pharmacological interventions should be performed to allow alternative pathway excretion of excessive nitrogen.** These include nitrogen scavenger therapy (sodium phenylacetate and sodium benzoate). Deficient urea cycle intermediates need to be replaced, which can include arginine (IV infusion) and/or citrulline (oral preparation). In patients with NAGS deficiency, replacement of n-acetylglutamate with the analog molecule carbamyl glutamate (or also known as Carbaglu® (carglumic acid)) can improve clinical symptoms. CARBAGLU should be added to the treatment regimen in a patient without a clear diagnosis at initial presentation [Dosing in adults and children is 100 mg/kg/day to 250 mg/kg/day divided into two to four doses] (Ah Mew et al 2015).
- **Treat catabolic state with calories from glucose, fats, and essential amino acids.** Complete restriction of protein should not exceed 12-24 hours because depletion of essential amino acids results in protein catabolism and nitrogen release. Enteral nutrition is preferred; however parenteral nutrition is an option. Placement of a nasogastric tube is needed for administration of essential amino acids, infant formula, and administration of cofactors like CARBAGLU. Other strategies to combat catabolism include low-dose continuous infusion of insulin with maintenance of glucose delivery (Ah Mew et al 2015 and Haberle, et al 2012).

- **Reduce the risk for neurologic damage.** Intravenous fluids (10% glucose infusion) should begin with appropriate electrolytes) for physiologic stabilization, cardiac pressors as necessary, and treatment of subclinical seizures (Ah Mew et al 2015 and Haberle, et al 2012).

Long-term Treatment of Manifestations. The goal of treatment is to achieve normal development and to prevent hyperammonemia while providing good quality of life and avoiding side effects and complications. This is accomplished by decreasing nitrogen load with dietary restriction of protein, and using nitrogen scavengers (phenylbutarate and sodium benzoate) to provide alternative routes for nitrogen dispersal. Prompt replacement of citrulline or arginine may be necessary. CARBAGLU may be used to promote normal or near normal function of the CPS1 enzyme in NAGS deficiency (Ah Mew et al 2015 and Haberle, et al 2012).

Liver transplantation is the only curative treatment preventing further hyperammonemic crises, allowing normal diet, and stopping drug administration. It should be performed in a patient without severe neurological damage, while in a stable metabolic condition (Haberle, et al 2012).

2.7.1 TREATMENT OF NAGS DEFICIENCY WITH CARBAGLU® (carglumic acid)

Monotherapy with CARBAGLU is the treatment of choice for NAGS deficiency (Haberle, et al 2012). It is currently the only available product indicated by the United States FDA as adjunctive therapy for the treatment of acute hyperammonemia due to NAGS deficiency and as maintenance therapy for the treatment of chronic hyperammonemia due to NAGS deficiency. Given orally, CARBAGLU acts as a substitute for the missing physiologic activator and thereby stimulates the enzyme CPS1, triggering the urea cycle and normalizing blood ammonia concentration (Tuchman 2008). Any episode of acute symptomatic hyperammonemia should be treated as a life-threatening emergency. Uncontrolled hyperammonemias can rapidly result in brain injury, brain damage, and death. Prompt use of all therapies necessary to reduce plasma levels is essential.

CARBAGLU 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) and for maintenance therapy for the treatment of chronic hyperammonemia due to the deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS). In the acute state of severe hyperammonemia due to NAGS deficiency, treatment for pediatric and adult patients with CARBAGLU is initiated at a dose of 100 mg/kg/day to 250 mg/kg/day. The total dose should be divided into 2 to 4 doses and rounded to the nearest 100 mg. Plasma ammonia levels are generally reduced within 24 hours, but it may take 2-3 days to recover to within normal ranges. During acute hyperammonemic episodes, concomitant administration of CARBAGLU with other ammonia lowering therapies, such as alternate pathway medications, hemodialysis, and dietary protein is recommended. The administration of ammonia scavengers, of L-arginine or L-citrulline and in NAGS deficiency, of carbamylglutamate is highly valuable for treating acute hyperammonemic decompensation. Citrulline and/ or arginine administration aims at maximizing ammonia excretion through the urea cycle. (Haberle, et al 2012).

Once the ammonia levels have normalized, doses may be adjusted to establish a long-term treatment regimen that targets normal plasma ammonia levels for the age of the patient. Based on limited data in 22 patients receiving maintenance treatment with CARBAGLU in a retrospective case series, pediatric and adult maintenance doses were usually less than 100 mg/kg/day. During maintenance therapy the concomitant use of other ammonia lowering therapies and protein restriction may be reduced or discontinued based on plasma ammonia levels.

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 treatment with CARBAGLU is crucial to assess patient response to treatment.

Contraindications: None

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.

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

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

3.0 PRODUCT INFORMATION

3.1 GENERAL INFORMATION

Carbaglu® (carglumic acid) was approved by the US Food and Drug Administration (FDA) in 2010 for the adjunctive therapy for the treatment of acute hyperammonemia due to NAGS deficiency and for the maintenance therapy for the treatment of chronic hyperammonemia due to NAGS deficiency.

The marketing authorization for CARBAGLU is held with Orphan Europe Sarl (Paris, France), part of the Recordati Group.

CARBAGLU is distributed in the United States by Recordati Rare Diseases, Inc. (Lebanon, New Jersey), part of the Recordati Group.

3.2 COMPOSITION OF CARBAGLU TABLETS

Each CARBAGLU tablet contains 200 mg carglumic acid as active substance and is presented as a white elongated tablet (size 18.0 x 6.0 mm), scored on both sides and coded "C" on one side. It is available in 2 different pack sizes: 5- and 60-tablet bottles (see also Section 3.3).

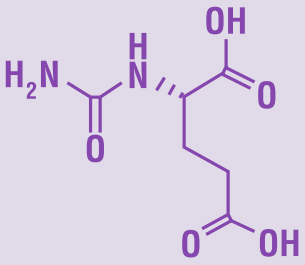
Name of ingredients	Function	Formula per tablet	Quantity per 5-tablet container	Quantity per 60-tablet container
Active substance: Carglumic acid	active substance	200 mg	1000 mg	12000 mg
Excipients:				
Microcrystalline cellulose	binder	270 mg	1350 mg	16200 mg
Sodium lauryl sulfate	wetting agent	0.5 mg	2.5 mg	30 mg
Hypromellose	binder	4 mg	20 mg	240 mg
Croscarmellose sodium	disintegrating agent	19 mg	90 mg	1140 mg
Silica, colloidal anhydrous	glidant	1.5 mg	7.5 mg	90 mg
Sodium stearyl fumarate	lubricant	5 mg	25 mg	300 mg
Purified water*	wetting agent	30 mg		
Total		**500 mg**	**2500 mg**	**30000 mg**

*substance disappearing during manufacturing

3.3 ACTIVE PHARMACEUTICAL INGREDIENT: CARGLUMIC ACID

CARBAGLU was developed as a new chemical entity by Orphan Europe, part of the Recordati Group, and is distributed in the United States by Recordati Rare Diseases. Carglumic acid is the International Non Proprietary Name (INN) of the active pharmaceutical ingredient (API) which was proposed by Orphan Europe and agreed on by the World Health Organization (WHO Recommended INN List 46).

General Information

Nomenclature	
INN:	Carglumic Acid
Chemical name:	N-carbamoyl-L-glutamic acid or (2S)-2-(carbamoylamino) pentanedioic acid
Structure	
Physical form:	White crystalline powder. Soluble in boiling water, slightly soluble in cold water, practically insoluble in organic solvents (cyclohexane, dichloromethane, ether).
Structural formula:	
Molecular formula:	$C_6H_{10}N_2O_5$
Relative molecular mass:	190.16
General Properties	
Appearance:	White powder or colorless crystals
Solubility:	Soluble in boiling water, slightly soluble in cold water, practically insoluble in organic solvents (cyclohexane, dichloromethane, ether)
Melting point:	159°C to 163°C
Chirality:	Carglumic acid is a chiral amino acid (L-isomer)
pH:	The pH of a 0.5% aqueous solution is between 2.2 and 3.2
pKa:	2.50, 3.55, 8.60
Log P:	2.14 at pH 3.0 and -1.93 at pH 7.4
Isomerism:	Carglumic acid prepared from L-glutamic acid, has an optical isomer N-carbamoyl D-glutamic acid.
Optical rotation:	The angle of optical rotation of a 1% aqueous solution of carglumic acid is [α]D=-6.0°±0.5°.
Polymorphism:	There is no enantiotropic polymorphism of carglumic acid

3.4 EXCIPIENTS

The excipients are microcrystalline cellulose, sodium lauryl sulfate, hypromellose, croscarmellose sodium, silica colloidal anhydrous and sodium stearyl fumarate. For safety reasons, no excipient from animal origin has been selected during the pharmaceutical development of the formulation.

All excipients are described in the European and US Pharmacopoeia and are tested for full compliance with their official monographs before the manufacture of the finished product.

3.5 DRUG PRODUCT

The finished product consists of tablets containing 200 mg of carglumic acid which are easily dispersible in water. The tablets are produced in strict compliance with the requirements of the Good Manufacturing Practices (GMP).

3.5.1 ROUTINE CONTROL TESTS OF THE DRUG PRODUCT

In addition to the verification of the general characteristics of the tablets (appearance, dimensions), the pharmaceutical tests cover uniformity of mass and disintegration time, in compliance with the methods described in the European and US Pharmacopoeia. A limit of 1 minute for the disintegration time was set in the interest of providing good dispersion. A dissolution test with a limit of minimum 90% dissolution within 15 minutes is also a part of the specifications. A procedure to test the fineness of the dispersion (until the end of shelf life) completes the pharmaceutical tests.

A second carglumic acid identification test in the tablets is performed by IR spectrophotometry. The quality specifications of Carbaglu® (carglumic acid) tablets at release are summarized below:

Specifications of CARBAGLU Tablets

Tests	Specifications
General characteristics	
Tablet appearance	White, bar-shaped tablets, scored on both sides and engraved on one side, size 18.0 x 6.0 mm
Pharmaceutical technical tests	
Uniformity of dosage units	L1=15.0; L2=25.0
Disintegration time	Complete disintegration within 1 min
Dissolution	90% within 15 min
Identification of carglumic acid	
HPLC retention time	Identical to reference
IR spectrum	Identity of the tablet spectrum minus placebo spectrum compared to the reference spectrum
D-enantiomer of carglumic acid	≤0.1%
Assay of carglumic acid	95.0%-105% of label claim (190 to 210 mg/tablet)
Tests for impurities	
Hydantoin-5-propionic acid	NMT 0.08%
Diaza-1, 3-dione-2,4-carboxy-7-cycloheptane	NMT 0.08%
Other impurities (individually)	NMT 0.10%
Total of impurities	NMT 0.75%
Water determination (moisture content)	≤5%
Microbial limits	
Total viable aerobic count	
Bacteria	≤1000 CFU/g
Yeast and mold	≤100 CFU/g
Test for specified microorganisms	
Escherichia coli	Absence in 1g of the product

HPLC: high performance liquid chromatography; IR: infrared; NMT: no more than

3.5.2 STABILITY STUDY RESULTS: DRUG PRODUCT

Unopened Tablet Containers

In addition to the routine tests performed for the release of the drug product, other tests were implemented during the stability studies in order to assess the pharmaceutical quality of the tablets: hardness, friability, water content (Orphan Europe, data on file). Breakability tests were also carried out at the beginning of the studies and were repeated at the end of the studies.

The stability results support a provisional shelf life of 36 months for the unopened commercially packaged product when it is stored at 2°C to 8°C (36°F – 46°F, in a refrigerator).

Opened Tablet Containers

A complementary stability study was conducted on the drug product after opening the tablet container (Orphan Europe, data on file). One tablet container of 3 different batches was opened for the first time after 12 month storage at 5°C. One tablet container was placed in a climatic chamber at 25°C + 60% RH and the other one in a climatic chamber at 30°C + 60% RH for 1 month. The third tablet container was stored during 1 month at room temperature and was opened and closed 3 times per day to mimic the condition of use of the product.

The tests performed did not reveal any important degradation phenomenon and support a storage period of up to 1 month after first opening of the tablet container, at a temperature below 30°C (86°F).

3.6 PACKAGING

Carbaglu® (carglumic acid) is available in 5 or 60 tablets in a polypropylene bottle with polyethylene cap and desiccant unit. The desiccant (white silica gel) is placed inside the stopper to prevent humidity problems due to the high amounts of disintegrating agent used in the formulation.

4.0 NONCLINICAL DATA

4.1 PHARMACOLOGY

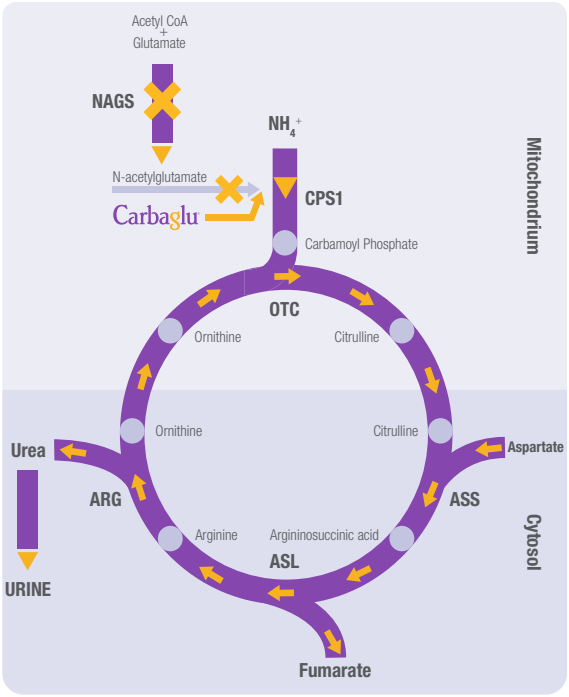
4.1.1 MECHANISM OF ACTION

The mechanism of action of Carbaglu® (carglumic acid) is based on the structural similarity of carglumic acid with NAG and its ability to replace NAG as an activator of mitochondrial CPS1, the first enzyme of the urea cycle.

4.1.2 IN VIVO STUDIES

Evidence for pharmacological efficacy of carglumic acid in the treatment of hyperammonemia is based on the treatment of normal or partially hepatectomised rats receiving potentially lethal doses of ammonia, as reported in the following 2 publications:

- Kim et al. (1972) found that 1 mmol/kg of intraperitoneally administered carglumic acid protected 61% of rats after lethal intravenous dose of ammonium acetate (10.8 mmol/kg), and 4 mmol/kg of carglumic acid protected 85% of these rats.
- Lee et al. (1998) performed a similar type of experiment in partially hepatectomized rats injected with ammonium acetate (3.4 mmol/kg). After administration of carglumic acid (1 mmol/kg) there was a decrease in ammonia levels to 278.09±60.02 µmol/L compared to 415.72±166.38 in the control group ($p<0.05$). The correlation between blood ammonia level and behavioral abnormalities observed in hepatic encephalopathy was also investigated.



Enzymes of the Urea Cycle:
NAGS: **N-acetylglutamate synthase**
CPS1: **carbamoyl phosphate synthetase 1**
OTC: **ornithine transcarbamylase**
ASS: **argininosuccinate synthetase**
ASL: **argininosuccinate lyase**
ARG: **arginase**

Concerning the behavioral grading scores, the results after carglumic acid alone were 1.09±0.30 compared to 2.54±1.36 in the control group ($p<0.01$). Thus the protective effect on the behavioral change significantly correlated with their effects on blood ammonia level.

In both studies, rats received carglumic acid combined with arginine. Results showed that arginine increased the protective effect of carglumic acid against ammonia intoxication. It is suggested that this potentialization by arginine might be due to an increase in the synthesis of NAG. In clinical use for the treatment of NAGS deficiency, this theoretical potentialization would therefore be dependent on the level of residual enzyme activity. As the benefit of arginine has not been so far confirmed in clinical practice, the concomitant use of arginine cannot be systematically recommended but this option is left open to the clinician.

Another study found that the mitochondrial membrane is more permeable for carglumic acid than for NAG (Rubio 1981). The differential penetration into mitochondria in favor of carglumic acid was demonstrated in mice models where ^{14}C-labeled NAG could not be detected in liver mitochondria but ^{14}C-labeled carglumic acid could be found.

4.2 PHARMACOKINETICS

The pharmacokinetic (PK) profile of carglumic acid was determined based on 2 studies using radiolabelled carglumic acid: 1 study was conducted in rats after single oral administration and 1 study was an in vitro study using human and rat hepatocytes (Orphan Europe, data on file).

In addition, toxicokinetic data collected during 2-week and 6-month repeated dose toxicity studies in rats as well as data from an absorption, distribution, metabolism and elimination (ADME) study in dogs were available to complete the information on the PK of carglumic acid (Orphan Europe, data on file). In these studies, carglumic acid was measured in plasma and urine samples using a validated liquid chromatographic-tandem mass spectrometry (LC/MS- MS) method, with a high level of sensitivity and specificity.

4.2.1 ABSORPTION

The absorption profile in rats showed a gender-independent T_{max} of between 2 and 4 hours, without a dose proportional AUC or C_{max} in the table below.

Evolution of C_{max} Versus the Administered Doses in Different Studies In Rats.

Daily doses (mg/kg)	Time of sampling	C_{max} (µg/ml)	
		Male	Female
250	Day 12 of the 2-week toxicity study	50.4	39.1
500	Day 1 of the 6-month toxicity study	76.7	68.7
1000	Day 1 of the 6-month toxicity study	85.9	95.5
500	End of the 6-month toxicity study	71.6	82.9

After repeated administration for 6 months, no accumulation phenomenon was shown in plasma.

4.2.2 METABOLISM

The metabolic profile was addressed in vitro (on cultures of human and rat hepatocytes) and in vivo (in rats with ^{14}C carglumic acid) and did not reveal any metabolite formation. Nevertheless, in rats given a single oral dose of 500 mg/kg ^{14}C carglumic acid, 51%, 37% and 9% of the radioactivity has been shown to be eliminated within 96 hours by urine, feces, and CO_2, respectively. Therefore it is assumed that a low level of metabolization of carglumic acid should occur in vivo, leading to a total breakdown of the molecule into CO_2 even if no intermediate such as ^{14}C-glutamic acid or any other potential metabolite was detected under the experimental conditions.

Preliminary comparative analysis of the preclinical and clinical information on Carbaglu® (carglumic acid) metabolism could have led to the conclusion that there may be some potential differences in the metabolite profiles of carglumic acid in rats and humans with regards to the formation of HPA. This molecule is a cyclization by-product of the drug substance, whose level in the drug product is strictly controlled in order to remain below or equal to 0.1% m/m; it is also a known metabolite of histidine catabolism, in particular in rats and humans,

and was investigated as a potential metabolite of carglumic acid. The assay of HPA by LC/MS-MS in plasma of healthy volunteers showed that some volunteers had quantifiable amounts of HPA in a few samples collected after dosing with Carbaglu® (carglumic acid), which could be interpreted as evidence that HPA is a metabolite of carglumic acid, at least in small amounts in humans. There was no convincing evidence of metabolization of carglumic acid into HPA as no PK profile of this potential metabolite was detected but only isolated fluctuations of this compound produced endogenously via histidine metabolism.

An absorption, distribution, metabolism, and elimination study of carglumic acid after oral and intravenous administration was performed in dogs. A cross species comparative analysis of the preclinical and clinical information available was also done.

The conclusion on CARBAGLU metabolism is that the PK properties fit well between the 3 species (rats, dogs, and humans).

4.2.3 ELIMINATION

In rats, carglumic acid is eliminated mainly in urine (50%) and in feces (about 40%) as unchanged compound. Although no circulating metabolite was detected, a small percentage of the total radioactivity was found to be eliminated as expired CO_2 (about 9%, 72 hours post- dose). The elimination is biphasic with a first rapid elimination phase in which about 70% of the dose is eliminated during the first 12 hours. The total excretion in rats accounts for about 97% of the administered dose after 96 hours. Toxicokinetic data showed that $T_{1/2}$ is about 3 to 3.5 hours whatever the administered dose in rats.

4.3 SAFETY PHARMACOLOGY

Three safety pharmacology studies conducted by Orphan Europe evaluated the effects of carglumic acid on the behavior and body temperature in the rat (Irwin test), on respiratory parameters in the rat, and on the cardiovascular system in the dog (Orphan Europe, data on file).

These studies did not reveal any relevant effects following single dose administration up to 1000 mg/kg of carglumic acid in both species. In addition, an in vitro study on isolated canine Purkinje fibres (Orphan Europe, data on file) confirmed the absence of cardiovascular effects, in particular on action potential duration of carglumic acid.

4.4 TOXICOLOGY

4.4.1 GENERAL TOXICOLOGY

Based upon clinical experience, the treatment with CARBAGLU may be started as early as the very first day of life. Therefore toxicology studies were deliberately designed with consideration for dosing of infants and children. The general toxicological profile for CARBAGLU was addressed through single dose toxicity studies and repeated dose toxicity studies in rodents.

The repeated dose toxicity study program involved one study in newborn rats, administered from the 4th to the 21st day of life and one 6-month study in juvenile/young adult rats, with interim evaluation at 3 months and including satellite groups of animals treated 4 weeks for micronucleus testing. Moreover, immunotoxicity endpoints and cell proliferation evaluation in selected organs were incorporated in the study.

4.4.2 ACUTE TOXICITY STUDIES

Single dose toxicity studies were performed in the rat via oral and intravenous administration (Orphan Europe, data on file).

Single doses of carglumic acid up to 2800 mg/kg orally and 239 mg/kg intravenously administered did not induce any mortality or abnormal clinical signs in adult rats. There were no variations of body weight and no abnormalities observed at necropsy.

4.4.3 REPEATED DOSE TOXICITY STUDIES

The repeated dose toxicity program includes 2 studies in the rat (Orphan Europe, data on file); a subacute toxicity study performed in newborn rats to address the intended use in the first part of life, and a chronic 6-month study in rats to address the planned long term exposure.

In the newborn rats receiving daily carglumic acid by oral gavage for 18 days as well as in the young rats receiving daily carglumic acid for 26 weeks, the No Observable Effect Level (NOEL) was established at 500 mg/kg/day and the No Observed Adverse Effect Level (NOAEL) was established at 1000 mg/kg/day.

A low level of metabolization was observed in vivo in rats. This level was too low to enable the detection of any metabolite explaining the metabolic pathway into expired CO_2 but with reassuring bioassay results in human plasma demonstrating that HPA, the main impurity of Carbaglu® (carglumic acid), is unlikely to be one of its metabolites.

4.4.4 GENOTOXICITY

A complete battery of genotoxicity studies was performed on carglumic acid and its 2 impurities hydantoin-5-propionic acid (HPA) and diaza-1,3-dione-2,4-carboxy-7-cycloheptane (Diaza) at high doses (Orphan Europe, data on file).

- Carglumic acid was tested for Ames test, bacterial reverse mutation test, in vitro chromosome aberration in human lymphocytes test, rat erythrocyte micronucleus test in bone marrow, without treatment and after 4 week treatment by oral route (gavage) in rats, up to 1000 mg/kg/day
- Diaza was tested for Ames test.
- HPA was tested for Ames test, chromosome aberrations by in vitro human lymphocytes metaphase analysis, in vivo study using the micronucleus test in mice up to 2000 mg/kg/day.

All those studies demonstrated that carglumic acid and its 2 impurities HPA and Diaza are devoid of genotoxic potential (Orphan Europe, data on file).

4.4.5 CARCINOGENICITY

The carcinogenic potential of carglumic acid has not been evaluated. However, carglumic acid does not have structural analogy with known carcinogens. In addition, there were no immunotoxicity, genotoxic, or immunodepressive properties based on a battery of mutagenicity tests (Orphan Europe, data on file) and tests on rats treated with carglumic acid for 6 months. There was no cell proliferation or signs of hyperplasia in the tissues and organs of rats after chronic administration (Orphan Europe, data on file).

4.4.6 REPRODUCTION TOXICITY STUDIES

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.

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).

5.0 CLINICAL DATA

5.1 PHARMACODYNAMICS

The mechanism of action of Carbaglu® (carglumic acid) is based on the structural similarity with NAG and its ability to replace the NAG function as activator of CPS1. CARBAGLU is able to restore the activity of the urea cycle, to normalize plasma ammonia levels, which are abnormally elevated in NAGS deficiency patients, and to finally restore ureagenesis (O'Connor 1985).

Short term administration of CARBAGLU rapidly restores the ureagenesis capacity in patients with NAGS deficiency to normal. (Caldovic 2004, Tuchman 2008). This effect correlated with:

- Normalization of both plasma ammonia and glutamine levels
- Markedly increased urea production

The authors studied patients with NAGS deficiency and one subject heterozygous for the disorder prior to and after 3 days of CARBAGLU treatment (2.2 g/m^2/day). One patient and her heterozygous mother were studied with the [^{15}N] tracer and another patient with the [^{13}C] tracer incorporated as the principal surrogate marker. The results confirmed restoration to control levels of markedly deficient ureagenesis following the administration of CARBAGLU, and suggested that the [^{13}C] tracer method is reliable even if it does not contain ammonia and labels urea more slowly than [^{15}N].

In conclusion, these results are consistent with a complete restoration of ureagenesis shortly after the initiation of treatment. The published experience (Caldovic 2004, Tuchman 2008) and the observations in NAGS deficiency patients treated with CARBAGLU show a quick, significant and steady decrease in the key biological response markers, ammonemia and glutaminemia, in response to the specific treatment.

5.2 PHARMACOKINETICS

5.2.1 PHARMACOKINETICS IN HEALTHY VOLUNTEERS

A PK study was conducted in 12 healthy male adults after a single oral administration of 100 mg/kg in order to determine plasma concentrations and urine excretion of carglumic acid (Orphan Europe, data on file). A specific and highly sensitive assay method was developed and validated for carglumic acid determination using HPLC coupled with tandem mass spectrometry.

Pharmacokinetic Parameters for the Carbaglu® (carglumic acid) Tablet

Pharmacokinetic parameter	Median	Range
Time to peak plasma concentration	3 hours	(2 – 4)
Peak plasma concentration	2.6 µg/mL	(1.8 – 4.8)
Apparent volume of distribution	2657 L	(1616 – 5797)
Terminal half-life	5.6 hours	(4.3 – 9.5)
Apparent total clearance	5.7 L/min	(3.0 – 9.7)
Renal clearance	290 mL/min	(204 - 445)

The inter-subject variability was moderate (coefficients of variation around 30% for most parameters). Carglumic acid peaked in plasma after a few hours suggesting an active transport through the intestinal mucosa. The oral bioavailability of carglumic acid was low, probably due to weak intestinal absorption and not because of extensive liver uptake. Another open label study (Orphan Europe, data on file) with ^{14}C-labelled carglumic acid investigated the mass balance, PK and metabolism following a single oral administration of 70 µCurie ^{14}C-labeled carglumic acid (100 mg/kg) in 3 healthy male subjects. The metabolic capacity of carglumic acid was demonstrated to be limited in at least 2 out of the 3 subjects (Orphan Europe, data on file). The parent compound assayed was shown to be excreted in large amounts in feces (approximately 60% in Subjects 001 and 003 but only 8.5% in Subject 002), and to a lesser extent in urine (approximately 9%). These results accurately matched the radioactivity amounts excreted in feces (approximately 72% in Subjects 001 and 003 but only 16.5% in Subject 002) and perfectly matched the radioactivity amounts excreted in urine (approximately 9%).

The plasma elimination curve of carglumic acid was biphasic with a rapid phase over the first 12 hours post dosing followed by a slow phase from 12 to 72 hours (no detectable concentration of the parent compound after this time point). The apparent terminal half-life was estimated to be around 21 hours. The plasma profile of carglumic acid only matched the first peak of radioactivity.

5.2.2 PHARMACOKINETICS IN NAGS DEFICIENCY PATIENTS

Carglumic acid plasma levels were measured in 11 NAGS deficiency patients (Orphan Europe, data on file). The age of these patients ranged from 1 day to 13 years and the daily dose given ranged from 7.4 to 122.3 mg/kg. Blood was collected at trough and/or anticipated peak (around 3 hours post-dose) times.

The range of plasma concentrations measured in these patients, including newborn infants, was consistent with the data obtained in healthy adults.

5.2.3 CONCLUSIONS

The results of the PK analyses found that:

- The apparent volume of distribution was 2657L (range:1616-5797). Protein binding has not been determined.
- After single oral administration, C_{max} was achieved in 2-4 hours in both healthy and NAGS deficiency patients.
- In humans, after a single oral dose of 100 mg/kg of body weight, carglumic acid was mainly eliminated as the unchanged compound in feces (around 60%) and to a much lesser extent in urine (9%).

5.3 EFFICACY

5.3.1 RETROSPECTIVE STUDY DESCRIPTION

(Orphan Europe, data on file)

Due to the rare and serious nature of the disease, Orphan Europe assessed the efficacy of Carbaglu® (carglumic acid) based on data from uncontrolled, retrospective case series.

Orphan Europe conducted a retrospective study using data collected from 23 NAGS deficiency patients (14 males and 9 females) who received treatment with CARBAGLU and who started treatment before December 2007 (the cut-off date for safety data collection was December 2008).

The primary objective was to review the clinical and biological response of NAGS deficiency patients to CARBAGLU within the first 7 days of treatment (short term) and at the last report (long term). For the short term analysis, ammonemia was the primary biomarker supported by glutaminemia and citrullinemia results. For the long term analysis all 3 biomarkers, ammonemia, glutaminemia and citrullinemia, were considered equally.

The secondary objectives were the evaluation of the clinical development, ie, neurological and psychomotor status, and anthropometric development (growth) parameters; the analysis of the implementation of a restrictive/protein-free diet and concomitant treatment; the analysis of the CARBAGLU doses prescribed as an indirect efficacy parameter and as a definition of the dose response determination.

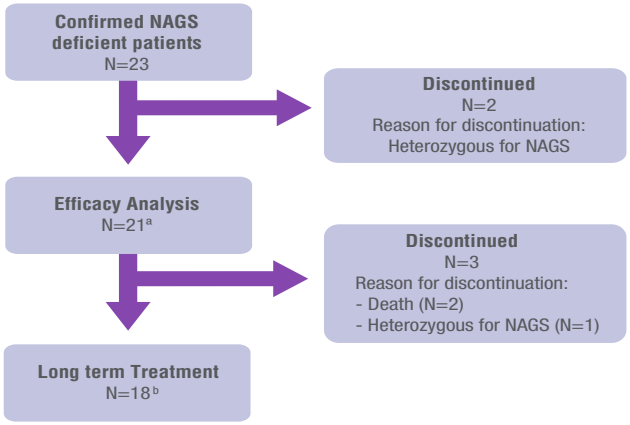
This report also included a short PK analysis and a short description of safety data.

Out of the 23 patients, 18 (78.3%) were under long term continuous treatment with CARBAGLU and provide data to support the claim for the indication of CARBAGLU in the management of NAGS deficiency (pg 27). In total, 5 patients discontinued treatment: 3 patients had confirmation of a heterozygote NAGS gene mutation by DNA testing, and 2 patients died (see Section 5.3.5).
The age at initiation of treatment was heterogeneous: 9 patients started at <1 month of age, 9 patients between 2 and 11 months of age, and 5 patients between 1 and 13 years of age.

5.3.2 DIAGNOSIS

Diagnosis of NAGS deficiency was confirmed by DNA testing in 19 of the 23 patients, all of which were performed in the same laboratory.

Study Population of the Retrospective Study



NAGS = N-acetylglutamate synthase; **N** = Number of patients.

A. The development of ammonemia was assessed in 20 patients, since 1 patient had no ammonia level reported prior to treatment with Carbaglu® (carglumic acid).

B. One of these patients was previously diagnosed and treated as a patient with CPS1 deficiency until a DNA confirmation of NAGS homozygous mutation.

5.3.3 CARBAGLU TREATMENT

Data available on dosing of CARBAGLU were assessed relative to short term and long term treatment. Analysis of short term treatment showed that daily doses were between 100-250 mg/kg during the first few days, administered 2 to 4 times a day. The dose was then slowly reduced over time depending upon the biological response. Extremely low doses were associated with failure to prevent metabolic decompensation.

The study showed a trend toward maintenance of the initial dose in the first few days after starting treatment. Those patients who started with a relatively high daily dose of CARBAGLU and responded positively to the treatment were slowly treated with relatively lower CARBAGLU doses.

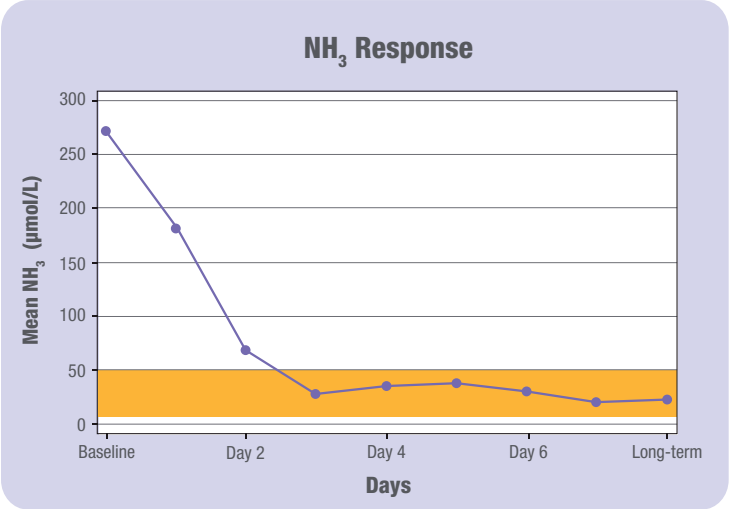
At the cut-off date for the efficacy analyses (December 31, 2007) the duration of treatment ranged from 7.4 months to 248.5 months (20.7 years). With the exception of 2 patients, the duration of exposure to CARBAGLU for the majority of patients exceeded 1 year. Most patients had a long term exposure to CARBAGLU for ≥5 years (14 out of 23 patients).

Concomitant treatments were specific amino acids, ammonia scavengers and hemodialysis. Hemodialysis was administered only as a rescue therapy during a hyperammonemic crisis in 4 patients.

Diet analysis showed that the majority of patients quickly changed from a protein-restricted diet to a normal protein intake upon CARBAGLU initiation, with the exception of 1 patient who was kept on a mildly protein-restricted diet on a long term basis.

5.3.4 EFFICACY RESULTS

Ammonia Response for 13 Evaluable NAGS Deficiency Patients at Baseline and After Treatment With Carbaglu® (carglumic acid)

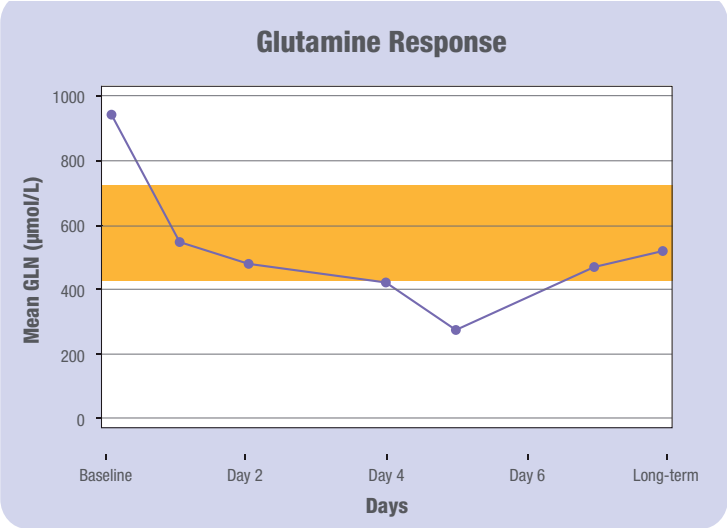


Plasma ammonia concentrations, measured in 20 patients, showed a significant and rapid decrease in pathological plasma ammonia levels to normal ranges. Plasma ammonia reached normal levels within the first 24 to 48 hours after initiation of CARBAGLU treatment, with the exception of 1 patient whose extremely high baseline ammonia (>1400 µmol/L) only reached normal levels by Day 3. At the long term treatment evaluation, the ammonia levels were within the normal range in all patients receiving an adequate dose of CARBAGLU. Decompensations were only reported at the end of the data collection period in 2 patients due to inadequately low dosing.

Plasma Gln levels were elevated before CARBAGLU therapy in 16 patients, sometimes even despite sodium benzoate or phenylbutyrate treatment. They rapidly normalized within the first 24 to 48 hours of CARBAGLU treatment and were maintained with continuous CARBAGLU treatment.

Plasma citrulline levels were low in 13 patients before initiation of CARBAGLU treatment, as expected during hyperammonemic crisis, and normalized quickly after the first dose of CARBAGLU.

Reduction in Glutamine Levels on Treament With Carbaglu Over Time



At baseline, 7 of 10 patients (70%) presented with affected neurological status, only 2 of whom continued to have an affected neurological status at the long term evaluation. The other 5 patients who presented with affected neurological development at baseline had normal neurological development at the last follow-up. None of the non-affected patients (30%) at baseline developed affected neurological status at the long term evaluation.

The mean (95% confidence interval) change from baseline for height in the 16 patients with data was +0.5, (-0.1, +1.2) and the median change from baseline of +0.5. The mean (95% confidence interval) change from baseline for weight in the 16 patients with data was +1.9, (+0.4, +3.4) and the median change from baseline of +0.9. These results show an improvement in height development and weight over time with CARBAGLU treatment.

5.3.5 PUBLISHED DATA

- The first patient with NAGS deficiency described in the literature and treated with carglumic acid started the treatment in 1980 on his 10th day of life* (Bachmann 1981, 1982; Schubiger 1991). Two male siblings had previously died within the first 2 weeks of life and hyperammonemia had been suspected in the second case. In the neonatal period, the patient was adhered to regimen that involved restriction of protein intake, sodium benzoate infusions, and adequate caloric supply with glucose infusions. An accidental withdrawal of the benzoate supply led to hyperammonemia with coma, muscular hypotonia, and a respiratory insufficiency which necessitated prolonged artificial ventilation. Carglumic acid was then started at a daily dose of 100 mg/kg allowing withdrawal of sodium benzoate and increase of alimentation. An initial increase to a daily dose of 750 mg/kg led to the clinical picture of a sympathomimetic-like reaction: tachycardia, profuse sweating, bronchial hypersecretion, increased body temperature and persistent crying. At the age of 13.5 months the boy was discharged fromthe hospital with the following therapy: enteral nutrition (1.5 g of protein/d), carglumic acid (180 mg/kg/d) and arginine. He was already developmentally delayed with pronounced muscular hypotonia. During his 9 years of life, he required 7 hospitalizations of short duration due to metabolic relapses usually caused by changes in nutrition or febrile infections. On several occasions increased transaminases were detected. The somatic development progressed along the 50th percentiles and the psychomotor development remained delayed. In 1990, the patient died at the age of 9.5 years after an episode of coma and generalized convulsions despite successfully lowering ammonia level by sodium benzoate infusion; the cause of death was not clearly elucidated and the relation to treatment was not assessable.

- Another publication (Hinnie 1997) reported the case of a 20-year-old patient with NAGS deficiency from the United Kingdom (UK) who had been hospitalized on several occasions for hyperammonemia since the age of 1.5 years. During the last admission for severe hyperammonemia secondary to febrile illness, he developed pneumonia and generalized convulsions. Hemodialysis was performed for 5 weeks in order to control ammonia levels, during which time he developed 2 episodes of septicemia. Carglumic acid was introduced at a daily dose of 60 mg/kg following cessation of hemodialysis because ammonia levels rose again above 100 µmol/L. The patient has subsequently maintained levels around 20-60 µmol/L and has been crisis free for 2 years on carglumic acid and arginine. Unfortunately, he has been left with gross cerebral dysfunction and paraplegia with incontinence; prior to the last episode he had been fully ambulant with normal somatic development.

- One case of neonatal NAGS deficiency was also reported in the UK (Morris 1998). At 4 months of age, the patient was started on a daily dose of carglumic acid (100 mg/kg) which allowed an increase in daily protein intake to 2.5 g/kg and a reduction in sodium benzoate dosage. At 20 months of age the patient had no neurological or developmental abnormalities and had experienced only one hyperammonemic episode precipitated by otitis media.

- Another case of neonatal NAGS deficiency was reported in the Netherlands. This neonate was rescued from (Huijmans 1998) was rescued from neonatal hyperammonemic coma by peritoneal dialysis, sodium benzoate and arginine infusions; he was then started on a daily dose of carglumic acid of 100 mg/kg at the 10th day of life. Blood ammonia completely normalized, even upon increasing the daily protein intake up to 3 g/kg. His mental and motor development was normal at the age of 1.3 years.

- Another case of neonatal NAGS deficiency was reported in Sweden (Nordenström 2007). At the 3rd day of life, the patient was rescued from hyperammonemic coma with restriction of oral food intake, infusions of glucose, sodium benzoate and arginine. At the 4th day of life, carglumic acid was given

orally at a daily dose of 200 mg/kg, divided in 3 doses and veno-venous hemodiafiltration was initiated. Due to technical problem, the hemodiafiltration was discontinued for 4 h, resulting in increasing ammonia levels (from 984 to 1187 µmol/L). On the 5th day of life, the ammonia level started to decrease and reached normal levels about 36 hours after the initial dose of carglumic acid. Protein intake was gradually increased. Sodium benzoate and carglumic acid were gradually decreased and completely stopped at 13 days of age. After feeding difficulties and elevated ammonia levels, sodium benzoate and carglumic acid were reintroduced. Carglumic acid therapy was maintained at a daily dose of 50 mg/kg with normal plasma ammonia levels and a moderate protein-restricted diet was introduced after 5 months of age. At 2.5 years of age, the patient had normal psychomotor development.

- Another case of neonatal NAGS deficiency was reported in Germany (Gessler 2010). The patient developed slight hyperammonemia on the 3rd day of life and was treated with carglumic acid before confirmation of NAGS deficiency. (One younger sibling had previously died due to hyperammonemia in the neonatal period and another younger sibling who developed hyperammonemia on the 2nd day of life, was treated with arginine hydrochloride, sodium benzoate and protein restriction. After NAGS deficiency was suspected by enzyme analysis in the second sibling, sodium benzoate was replaced by carglumic acid. At 10 years of age, this sibling tested heterozygous for NAGS and carglumic acid treatment was stopped without deterioration of urea cycle function). After initiation of carglumic acid, the patient's diet was supplemented with sodium benzoate and arginine. After 4 hospitalizations for hyperammonemia within the 3 months of age, carglumic acid treatment was started at 3 months of age at a daily dose of 250 mg/kg, divided in 4 doses. Sodium benzoate and protein restriction were discontinued, whereas arginine supplementation was maintained. At 14 months of age, the daily dose of carglumic acid was adjusted to about 200 mg/kg. The patient did not develop hyperammonemia in the following years. NAGS deficiency was confirmed at 8 years of age. At 13 years of age, the patient had normal neurological development.

5.4 SAFETY

5.4.1 CLINICAL SAFETY IN NAGS DEFICIENCY PATIENTS

Up to cut-off date for the safety analysis, December 31, 2008, 18 of the 23 patients suffering from NAGS deficiency in the retrospective study had experienced an adverse event (AE).Because these AEs were reported retrospectively, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

In total, 120 AEs were reported including 37 serious adverse events (SAEs) and 83 non-serious AEs. The reported AEs were mainly from 3 system organ classes: gastrointestinal disorders (21%), infections and infestations (19%), and nervous system disorders (14%). The most common adverse reactions in ≥ 13% of patients treated with Carbaglu® (carglumic acid) are: infections, vomiting, abdominal pain, pyrexia, tonsilitis, anemia, ear infection, diarrhea, nasopharyngitis, and headache.

Two patients died due to an AE in the retrospective study. One patient died due to multiple organ failure. This patient showed poor compliance and, 1 month prior to the death, the daily dose of carglumic acid was reduced to 5 mg/kg, which was not in accordance with the recommended maintenance dose. Furthermore, a few days prior to the death, the patient experienced severe pneumopathy resulting in multiple organ failure. The second patient died due to a severe episode of hyperammonemia. The daily dose of carglumic

acid was very low at 6 mg/kg, which was not in accordance with the recommended maintenance dose. Neither of the fatal events was related to Carbaglu® (carglumic acid).

In addition to the 2 above-mentioned NAGS deficiency patients who died, 9 other patients experienced an SAE, none of which were related to CARBAGLU. These SAEs were mostly reported in 2 system organ classes: gastrointestinal disorders (10 SAEs, of which 6 were vomiting) and nervous system disorders (10 SAEs). The remaining SAEs were distributed in other system organ classes. None of the SAEs were considered as "related" to carglumic acid by the reporters.

Among the 83 non-serious AEs, only 1 was considered as "related" to carglumic acid by both the reporter and Orphan Europe. The patient experienced "poor acceptance" (due to product acidity) a few days after the initiation of treatment. Following temporary discontinuation, the AE abated. After reintroduction, no similar event occurred. In addition, none of the NAGS deficiency patients permanently discontinued CARBAGLU due to an AE related to the treatment.

5.5 CONCLUSION OF CLINICAL ASPECTS

Although small, the patient population with confirmed NAGS deficiency that has been studied includes the majority of living patients known to be affected with NAGS deficiency in Europe, and therefore, it is representative.

The value of the retrospective NAGS deficiency data is represented by the long term (>187 patient-years) follow-up of the NAGS deficiency patients treated with CARBAGLU.

These data demonstrated:

- Good metabolic control was achieved, normalizing ammonia and glutamine levels in the reported patients within a few hours after the initiation of CARBAGLU treatment.
- In spite of common childhood infectious episodes, vaccinations, and even surgical operations under general anesthesia – all events which may easily trigger decompensation episodes in NAGS deficiency under classical therapy– an increase in plasma ammonia levels was very rare and, when it occurred, it was only minimal.
- It is important to maintain adequate doses of CARBAGLU. Clinical signs of decompensation were only observed on 2 occasions in patients receiving inadequate (very low) dosing.
- A normal protein intake or moderate protein restriction was possible in all patients treated with CARBAGLU.
- The need for arginine should be tested individually. Additional arginine supplementation was systematically given in a few patients but overall results in these patients were not different from those in patients who received Carbaglu only.
- No serious safety issue has been identified. The safety profile with the recommended dosage regimen was highly acceptable in NAGS deficiency patients. Routine hematology and blood chemistry tests did not show any abnormality that could be related to CARBAGLU therapy.

Carbaglu therapy offers a specific pharmacological therapy for the treatment of hyperammonemia due to NAGS deficiency: as adjunctive therapy for acute hyperammonemia and as maintenance therapy for chronic hyperammonemia (see CARBAGLU Prescribing Information).

5.6 RECOMMENDATIONS FOR CARBAGLU® (carglumic acid) USE

5.6.1 INDICATIONS AND USAGE

CARBAGLU is a Carbamoyl Phosphate Synthetase 1 (CPS 1) 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 are recommended.
- 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.

5.6.2 DOSAGE

CARBAGLU treatment should be initiated by a physician experienced in the treatment of metabolic disorders. Based on clinical experience, the treatment may be started as early as the first day of life. The recommended initial dose in pediatric and adult patients for acute hyperammonemia is 100 mg/kg/day to 250 mg/kg/day. Dosing should be titrated based on individual patient plasma ammonia levels and clinical symptoms.

In the long term, pediatric and adult maintenance doses should be titrated to target normal plasma ammonia levels for the age. Based on data from the retrospective study (see Section 5.3.1.2), daily maintenance doses were usually less than 100 mg/kg.

Based on PK data and clinical experience, it is recommended to divide the total daily dose into 2 to 4 doses, rounded to the nearest 100 mg (ie, half a CARBAGLU tablet), to be given before meals or feedings. The breaking of the tablets in halves allows most of the required posology adjustments. There is no concern for the safe use of half-tablets because the key element for the treatment of NAGS deficiency patients is the total daily dose of CARBAGLU.

5.6.3 PREPARATION AND ADMINISTRATION

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.

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.

Preparation for Oral Administration Using an Oral Syringe in Pediatrics

For administration via oral syringe, Carbaglu® (carglumic acid) 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.

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.

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

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

5.6.4 IMPORTANT SAFETY INFORMATION

Indications and Usage

CARBAGLU is a Carbamoyl Phosphate Synthetase 1 (CPS 1) 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 are recommended.
- 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.

Important Safety Information

HYPERAMMONEMIA :

- Management of hyperammonemia due to N-acetylglutamate synthase (NAGS) deficiency and Carbaglu® (carglumic acid) treatment should be initiated by a physician experienced in the treatment of metabolic disorders.
- 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.
- 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.

THERAPEUTIC MONITORING:

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

NUTRITIONAL MANAGEMENT:

- 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.

The most common adverse reactions in ≥ 13% of patients are: infections, vomiting, abdominal pain, pyrexia, tonsillitis, anemia, ear infection, diarrhea, nasopharyngitis, 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.

No drug interactions have been identified. There is no human pregnancy data, but decreased survival and growth occurred in animal offspring.

Breast feeding by a mother taking CARBAGLU is not recommended.

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

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7.0 CARBAGLU PRESCRIBING INFORMATION

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 the 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)
- The recommended maintenance dose should be titrated to target normal plasma ammonia levels for age (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)

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

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, tonsillitis, anemia, ear infection, diarrhea, nasopharyngitis, 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.

DRUG INTERACTIONS

No drug interactions have been identified. (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: 11/2015

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 of 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.

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

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
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.

6 ADVERSE REACTIONS

6.1 Retrospective Case Series Experience
The most common adverse reactions (occurring in ≥ 13% of patients), regardless of causality, are: Infections, vomiting, abdominal pain, pyrexia, tonsillitis, 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	
Infections	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
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.

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.

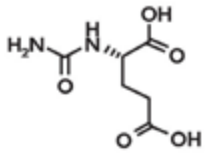
10 OVERDOSAGE
One patient treated with 650 mg/kg/day of carglumic acid developed symptoms characterized as a monosodium glutamate intoxication-like syndrome: tachycardia, profuse sweating, increased bronchial secretion, increased body temperature and restlessness. These symptoms resolved upon reduction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

12 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 have 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 value 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.

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

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 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 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.

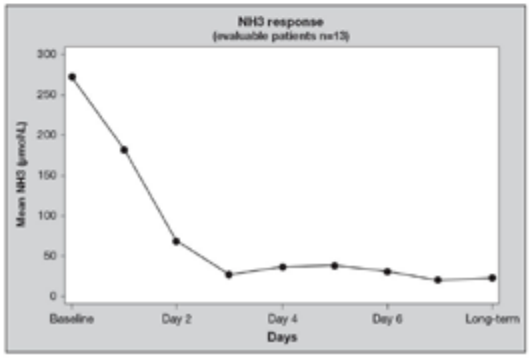
Table 3. Plasma ammonia levels at baseline and after treatment with Carbaglu®

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®



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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 52276-312-05 Bottles of 5 tablets

NDC 52276-312-60 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°C (36 to 46°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 infections, vomiting, abdominal pain, pyrexia, tonsillitis, anemia, ear infection, diarrhea, nasopharyngitis, and headache.

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Carbaglu
carglumic acid

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