PRODUCT INFORMATION

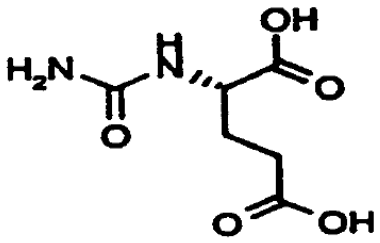
CARBAGLU®

NAME OF THE MEDICINE

Carglumic acid 200 mg dispersible tablets.

Carglumic acid is a white crystalline powder, soluble in boiling water, slightly soluble in cold water, practically insoluble in organic solvents (cyclohexane, dichloromethane, ether).

Its structural formula is:



Molecular formula: $C_6H_{10}N_2O_5$

Relative molecular mass: 190.16

DESCRIPTION

CARBAGLU is a dispersible tablet containing 200mg of carglumic acid (CAS No. 1188-38-1). The tablets are white and elongated and can be divided into equal halves.

CARBAGLU contains the following inactive ingredients: microcrystalline cellulose, sodium lauryl sulfate, hypromellose, croscarmellose sodium, anhydrous colloidal silica, sodium stearylfumarate.

PHARMACOLOGY

Pharmacodynamics

Mechanism of action

Carglumic acid is a structural analogue of N-acetylglutamate (NAG), which is the naturally occurring activator of carbamoyl phosphate synthetase 1 (CPS 1), the first enzyme of the urea cycle. N-acetylglutamate is the product of N-acetylglutamate synthase (NAGS). Where NAGS is defective, NAG synthesis is impaired and thus CPS 1 is not activated; consequently the urea cycle is not triggered. Carglumic acid has been shown *in vitro* to activate hepatic CPS 1. Although carglumic acid has a lower affinity for CPS than the naturally occurring NAG, *in vivo* it has showed more effective and longer lasting effect than NAG.

Pharmacodynamic effects

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

Pharmacokinetics

The pharmacokinetics of carglumic acid has been studied in healthy male volunteers using radiolabelled and unlabelled product.

Absorption

After a single oral dose of 100 mg/kg body weight, approximately 30% of carglumic acid is estimated to be absorbed. At that dose-level, in 12 volunteers given CARBAGLU tablets, plasma concentration peaked at 2.6 µg/ml (median; range 1.8-4.8) after 3 hours (median; range 2-4).

Absolute bioavailability of carglumic acid has not been determined.

Distribution

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

Protein binding has not been determined.

Metabolism

A proportion of carglumic acid is metabolised, possibly by the intestinal flora. One possible end product of carglumic acid metabolism is carbon dioxide, which is eliminated through the lungs.

Elimination

After a single oral dose of 100 mg/kg body weight, 9% of the dose is excreted unchanged in the urine and up to 60% in the faeces.

Plasma levels of carglumic acid were measured in patients of all age categories, from newborn infants to adolescents, treated with various daily doses (7 – 122 mg/kg/day). The ranges reported were consistent with those measured in healthy adults, including those from newborn infants. Regardless of the daily dose, plasma levels slowly declined over 15 hours to levels approximately 100 ng/ml.

CLINICAL TRIALS

NAGS Deficiency

In patients with N-acetylglutamate synthase (NAGS) deficiency, carglumic acid has been shown to induce a rapid normalisation of plasma ammonia levels, usually within 24 hours.

When the treatment was instituted before any permanent brain damage, patients exhibited normal growth and psychomotor development.

In a retrospective, non-comparative descriptive study, data was collected from NAGS deficiency patients treated with carglumic acid for the management of hyperammonaemia. Of the 23 patients reviewed, 18 were on long term continuous therapy with carglumic acid. The mean baseline biochemistry results are summarised in Table 1.

Table 1 Mean Baseline Biochemistry Results for NAGS Patients

Biomarker	Mean Plasma Concentration (SD)	N
Ammonia	218.9 µmol/L (299.0)	20
Glutamate	957.1 µmol/L (452.5)	16
Citrulline	19.8 µmol/L (16.5)	13
Urea	3.2 mmol/L (1.7)	15

Treatment with carglumic acid in NAGS comprised management of acute phase (initial 7 days), followed by long-term maintenance treatment. During acute treatment doses between 100 – 250 mg/kg/day administered 2 – 5 times per day were used. The dose was then reduced over time depending upon the clinical response, including laboratory monitoring.

Following treatment with carglumic acid in the acute phase, ammonaemia, glutaminaeia and citrulliaemia normalised quickly. Normal concentrations of these biomarkers were obtained 24 – 72 hours after the first dose of carglumic acid.

The demographic characteristics of the patient population are shown in Table 2.

Table 2 Baseline Characteristics of the 23 NAGS deficiency patients

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

Table 3 summarises the plasma ammonia levels at baseline, days 1 to 3 post-CARBAGLU treatment, and long-term CARBAGLU treatment for 13 evaluable patients.

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

Time point	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.

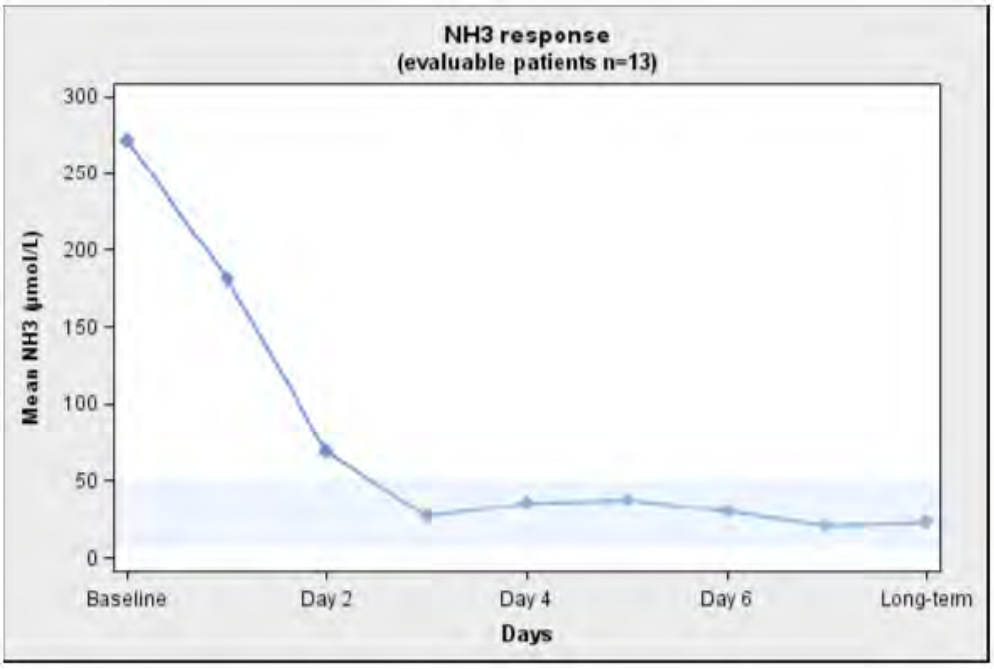


Figure 1 Ammonia response for 13 evaluable NAGS deficiency patients at baseline and after treatment with CARBAGLU

The analysis of long-term treatment with carglumic acid showed continuous control of ammonaemia, glutaminaemia, a discontinuation of the daily protein intake restriction, improvement in the growth parameters, neurological status and psychomotor status.

There were no decompensation events during treatment with carglumic acid as long as the dose administered was adequate. Extremely low doses for age and weight exposed patients to sudden metabolic status decompensation.

Organic Acidaemias

In patients with organic acidaemia (neonates and non-neonates), the treatment with carglumic acid induced a quick decrease of ammonia plasma levels, reducing the risk of neurological complications.

In an observational study, based on retrospective analysis of the outcomes from treatment with carglumic acid, the reduction in plasma ammonia levels was assessed in patients during organic acidaemia (OA) decompensation episodes. In total, 57 patients were enrolled, with 41 included in the efficacy analysis following the treatment with carglumic acid during the OA decompensation episode. Seven patients reported two or more episodes during the treatment phase. No pre-defined dose of carglumic acid was stated, however the standard recommended initial dose of carglumic acid is 100-250 mg/kg/day, given twice or thrice daily, which was taken as reference for data analysis. The primary endpoint assigned for the study was the reduction in plasma ammonia levels following carglumic acid treatment.

From the 41 patients included in the efficacy analysis, 4 (9.8%) were confirmed as isovaleric acidaemia (IVA), 21 patients (51.2%) were confirmed as methyl-malonic acidaemia (MMA),

and 16 patients (39.0%) as confirmed propionic acidaemia (PA). The baseline age of the episodes in the efficacy population was a median of 9.0 days. At the initiation of the treatment with carglumic acid, 29 episodes (out of 48) occurred during the first 4 weeks after birth (neonates) and 19 episodes occurred beyond the neonatal period (non-neonates).

The baseline ammonaemia recorded was a mean of 350.7 µmol/L (range: 76.0 to 1633.0 µmol/L) in the efficacy population.

Treatment with carglumic acid in IA was aimed at resolution of acute decompensation episode. The majority of episodes were initially treated with a dose of carglumic acid 100-250mg/kg/day. The duration of treatment ranged from 1 to 15 days with a mean of 5.5 days (5.2 days PA, 6.1 days MMA, 3.5 days IVA). The mean duration of treatment was 4.9 days in neonates and 5.3 days in non-neonates. A trend to decrease the dose from 1st to the last day (up to 15 days at the discretion of the treating physician) was seen as shown in Figure 2.

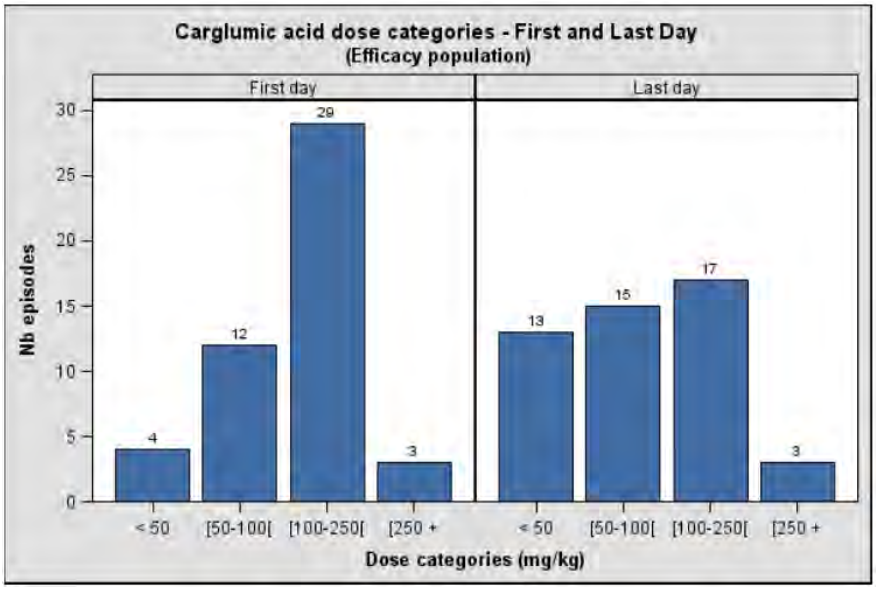


Figure 2 First and last day CARBAGLU dose in the general efficacy population

Following carglumic acid treatment, a significant biological response to the treatment with carglumic acid was observed, with the mean ammonaemia at primary endpoint of 58.5 µmol/L (range 15.0 – 58.0 µmol/L). The mean plasma ammonia concentrations decrease from baseline was -292.2 µmol/L with a reduction range from -24.0 to -1540.0 µmol/L. When ammonia scavengers were administered concomitantly with carglumic acid, the respective plasma ammonia levels at the endpoint were:

- with ammonia scavengers, a mean of 55.6 µmol/L, and
- without ammonia scavengers a mean of 60.8 µmol/L.

The mean time to achieve the primary endpoint was 2.4 days (58.7 hours), with this time equivalent in the disease category groups. The median time to achieve the primary endpoint for the three OA was:

- 40.5 hours for the IVA episodes,
- 37.5 hours for the MMA episodes and
- 36.0 hours for the PA episodes.

INDICATIONS

Carbaglu is indicated in treatment of

- Hyperammonaemia due to N-acetylglutamate synthase primary deficiency
- Hyperammonaemia due to Organic Acidaemias such as:
  - Hyperammonaemia due to isovaleric acidaemia
  - Hyperammonaemia due to methymalonic acidaemia
  - Hyperammonaemia due to propionic acidaemia

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

Breast-feeding during the use of carglumic acid is contraindicated.

PRECAUTIONS

Therapeutic monitoring

Plasma levels of ammonia and amino acids should be maintained within normal limits. Ongoing monitoring of neurological and cardiac status, laboratory tests (renal, hepatic, haematological) and clinical responses in patients receiving carglumic acid is crucial to assess patient response.

Cardiotoxicity and Hepatotoxicity

Due to the small dataset, any association between carglumic acid and cardiotoxicity or hepatotoxicity cannot be reliably determined. Therefore, cardiac and hepatic function monitoring is advised during treatment with carglumic acid.

Nutritional management

Protein restriction during acute phase and protein supplementation during maintenance phase may be indicated. Specialised advice may be sought.

Effects on fertility

No formal clinical studies have been conducted to assess the effects of carglumic acid on fertility. There were no effects on fertility or reproductive performance in female rats at oral doses up to 2000 mg/kg/day (resulting in 28 times the clinical AUC). In a separate study, mating and fertility were unaffected in male rats at oral doses up to 1000 mg/kg/day (resulting in 14 times the estimated clinical AUC at the maximum recommended human dose, MRHD).

Use in pregnancy (Category B1)
There are no adequate and well controlled studies or available human data with carglumic acid in pregnant women. In embryofoetal development studies, no adverse effects were observed in pregnant rats and rabbits that received oral carglumic acid during organogenesis at doses up to 2000 mg/kg/day and 1000 mg/kg/day, respectively. These doses resulted in exposures (AUC) 28 and 2.4 times the estimated clinical AUC at the MRHD.

Use in lactation
It is not known whether carglumic acid is excreted into human milk. Carglumic acid is excreted in the milk of lactating rats and an increase in mortality and impairment of body weight gain occurred in neonatal rats nursed by mothers receiving carglumic acid (refer to CONTRAINDICATIONS). Therefore, breast-feeding during the use of carglumic acid is contraindicated.

Use in the elderly
No data is available regarding the administration of carglumic acid in the elderly.

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

Carcinogenicity
Carcinogenicity studies have not been conducted.

INTERACTIONS WITH OTHER MEDICINES

No specific clinical studies have been performed to assess possible interactions. Based on *in vitro* studies, carglumic acid is not an inducer of CYP1A1/2, 2B6 or 3A4/5 enzymes and is not an inhibitor of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 or 3A4/5..

ADVERSE EFFECTS

NAGS Deficiency
The most common adverse events (occurring in ≥ 13% of patients), regardless of causality, are: infections, vomiting, abdominal pain, pyrexia, tonsillitis, anaemia, ear infection, diarrhoea, nasopharyngitis, and headache.

Table 4 summarises adverse events occurring in 2 or more patients treated with carglumic acid in the retrospective study.

Table 4 Adverse Events reported in ≥ 2 patients treated with CARBAGLU in the NAGS Deficiency Retrospective Study

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

Organic Acidaemias

The most common adverse events, regardless of causality, are anaemia, and thrombocytopenia.

Table 4 summarises adverse events occurring in 2 or more patients treated with carglumic acid in the retrospective study.

Table 5 Adverse Events reported in ≥ 2 patients treated with CARBAGLU in the Organic Acidaemia Retrospective Study

System Order Class Preferred Term	Number of Patients (%)
TOTAL	57 (100)
Blood and lymphatic system disorders	
Anaemia	3 (5.3 %)
Thrombocytopenia	3 (5.3 %)
Gastrointestinal disorders	
Diarrhoea	2 (3.5%)
Vomiting	2 (3.5%)
General disorders and administration site conditions	
Condition aggravated	2 (3.5%)
Hyperthermia	2 (3.5%)
Hypothermia	2 (3.5%)
Pyrexia	3 (5.3 %)
Infections and infestations	
Sepsis	2 (3.5%)
Investigations	
Cardiac murmur	2 (3.5%)
Oxygen saturation decreased	2 (3.5%)
Metabolism and nutritional disorders	
Hyperglycaemia	2 (3.5%)

For spontaneous cases, the most common adverse events are vomiting, diarrhoea and rash.

DOSAGE AND ADMINISTRATION

CARBAGLU treatment should be initiated under the supervision of a physician experienced in the treatment of metabolic disorders.

Any episode of acute symptomatic hyperammonaemia should be treated as a life-threatening emergency and may be started as early as the first day of life. Treatment of hyperammonaemia may require dialysis, preferably hemodialysis, to remove a large burden of ammonia. Uncontrolled hyperammonaemia can rapidly result in brain injury/damage or death, and prompt use of all therapies necessary to reduce plasma ammonia levels is essential.

Plasma levels of ammonia and amino acids should be maintained within normal limits. Ongoing monitoring of neurological and cardiac status, laboratory tests (renal, hepatic, haematological) and clinical responses in patients receiving carglumic acid is crucial to assess patient response.

CARBAGLU tablets should not be swallowed whole or crushed. Disperse CARBAGLU tablets in water immediately before use. CARBAGLU is for oral administration only.

Adult Dosage
The recommended initial dose for acute hyperammonaemia is 100 mg/kg/day to 250 mg/kg/day. Concomitant administration of other ammonia lowering therapies is recommended during acute decompensations. 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.

In the long-term, the dose should be individually adjusted to maintain adequate metabolic control (normal plasma ammonia).

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

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

As with the use in adults, the recommended maintenance dose should be titrated to target normal plasma ammonia level for age.

In the long-term, the dose should be individually adjusted to maintain adequate metabolic control (normal plasma ammonia).

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

Carglumic acid responsiveness test

It is recommended to test individual responsiveness to CARBAGLU before initiating any long term treatment. As examples

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

Administration:

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 5 – 10 mL of water and taken immediately. The suspension has a slightly acidic taste. 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 (5 – 10mL) and the contents swallowed immediately.

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

- Mix each 200 mg tablet in 5 – 10 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.

Based on pharmacokinetic data and clinical experience, it is recommended to divide the total daily dose into two to four doses to be given before meals or feedings. The breaking of the tablets in halves allows most of the required posology adjustments. Occasionally, the use of quarter tablets may also be useful to adjust the posology prescribed by the physician.

Oral Administration Using an Oral Syringe in Paediatrics

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.

Nasogastric Tube Administration in Paediatrics

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.

OVERDOSAGE

In one patient treated with carglumic acid, where the dose was increased up to 750 mg/kg/day, symptoms of intoxication occurred which can be characterised as a sympathomimetic reaction: tachycardia, profuse sweating, increased bronchial secretion, increased body temperature and restlessness. These symptoms resolved once the dose was reduced.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

CARBAGLU is a white, elongated tablet with three score marks and engraved on one side. The tablet can be divided into two halves.

CARBAGLU is supplied in 5- or 60- polypropylene tablet tube containers closed by a polyethylene cap with a desiccant unit.

Not all pack sizes may be marketed.

Storage Conditions
Store at 2 °C to 8 °C (Refrigerate. Do not freeze). Protect from light.

Once the tablet container has been opened, it must be used within 1 month. Store the opened container below 30 °C (do not refrigerate). Keep the container tightly closed in order to protect from moisture.

NAME AND ADDRESS OF THE SPONSOR

Emerge Health
Suite 3, Level 1, 2 Theatre Place
Canterbury Victoria 3126
Australia
Ph: +61 3 9077 4468
www.emergehealth.com.au

POISON SCHEDULE OF THE MEDICINE

Schedule 4

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

12 February 2015

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