SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

CARBAGLU 200 mg (dispersible tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dispersible tablet contains 200 mg of carglumic acid.

For the full list of excipients, see section 6.1.

Sugar free.

3. PHARMACEUTICAL FORM

Dispersible tablets.

A white, bar-shaped tablet, scored on both sides and engraved on one side (4 punches with the letter c), size 18,0 x 6,0 mm.

The tablet can be divided into equal dose parts.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CARBAGLU is indicated in treatment of:

- Hyperammonaemia due to N-acetylglutamate synthase primary deficiency.
- Hyperammonaemia due to isovaleric acidaemia.
- Hyperammonaemia due to methylmalonic acidaemia.
- Hyperammonaemia due to propionic acidaemia.

4.2 Posology and method of administration

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

Posology:

For N-acetylglutamate synthase deficiency:

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

The initial daily dose should be 100 mg/kg, up to 250 mg/kg if necessary.

It should then be adjusted individually in order to maintain normal ammonia plasma levels (refer to section 4.4).

In the long term, it may not be necessary to increase the dose according to body weight as long as adequate metabolic control is achieved; daily doses range from 10 mg/kg to 100 mg/kg.

Carglumic acid responsiveness test

It is recommended to test individual responsiveness to carglumic acid 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.

For isovaleric acidaemia, methylmalonic acidaemia and propionic acidaemia:

The treatment should start upon hyperammonaemia in organic acidaemia patients. The initial daily dose should be 100 mg/kg, up to 250 mg/kg if necessary.

It should then be individually adjusted in order to maintain normal ammonia plasma levels (refer to section 4.4).

Renal impairment:

Caution is advised when administering CARBAGLU to patients with impaired renal function.

Dosage adjustment is required according to GFR.

- Patients with moderate renal impairment (GFR 30-59 mL/min)
    - the recommended initial dose is 50 mg/kg/day to 125 mg/kg/day for patients presenting an hyperammonaemia due to NAGS deficiency or organic acidaemia,
    - In the long term use the daily dose will be in the range of 5 mg/kg/day to 50 mg/kg/day and should be adjusted individually in order to maintain normal ammonia plasma levels
- Patients with severe renal impairment (GFR ≤ 29 mL/min)
    - the recommended initial dose is 15 mg/kg/day to 40 mg/kg/day for patients presenting an hyperammonaemia due to NAGS deficiency or organic acidaemia,
    - In the long term use the daily dose will be in the range of 2 mg/kg/day to 20 mg/kg/day and should be adjusted individually in order to maintain normal ammonia plasma levels

Paediatric population:

The safety and effectiveness of CARBAGLU for the treatment of paediatric patients (birth to 17 years of age) with acute or chronic hyperammonaemia due to NAGS deficiency and acute hyperammonaemia due to IVA, PA or MMA have been established.

Method of administration:

This medicine is for oral use only (ingestion or via a nasogastric tube using a syringe, if necessary).

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 medical practitioner.

The tablets must be dispersed in a minimum of 5 – 10 ml of water and ingested immediately or administered by fast push through a syringe via a nasogastric tube.

The suspension has a slightly acidic taste.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Breastfeeding during the use of carglumic acid is contraindicated (refer to sections 4.6 and 5.3).

4.4 Special warnings and precautions for use

Therapeutic monitoring

Plasma levels of ammonia and amino acids should be maintained within normal limits.

As very few data on the safety of carglumic acid are available, systematic surveillance of liver, renal, cardiac functions and haematological parameters is recommended.

Nutritional management

Protein restriction and arginine supplementation may be indicated in case of low protein tolerance.

Use in patients with renal impairment

The dose of CARBAGLU must be reduced in patients with renal impairment (see section 4.2).

4.5 Interaction with other medicines and other forms of interaction

No specific interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safe use during pregnancy has not been established.

For carglumic acid no clinical data on exposed pregnancies are available.

Animal studies have revealed minimal developmental toxicity (refer to section 5.3). Caution should be exercised when prescribing to pregnant women.

Breastfeeding

Carglumic acid has been shown to be present in the milk of lactating rats (refer to section 5.3). Therefore, breastfeeding during the use of carglumic acid is contraindicated (refer to section 4.3).

Fertility

No data exists on the effect of carglumic acid on fertility.

4.7 Effects on ability to drive and use machines

No studies on the effects of carglumic acid on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Tabulated list of adverse reactions

Reported adverse reactions are listed below, by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10), common (≥1/100 to <1/10), uncommon (≥1/1 000 to <1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

- Undesirable effects in N-acetylglutamate synthase deficiency

Investigations	Uncommon: increased transaminases
Skin and subcutaneous tissue disorders	Common: increased sweating Not known: rash

- Undesirable effects in organic acidaemia

Cardiac disorders	Uncommon: bradycardia
Gastrointestinal disorders	Uncommon: diarrhoea, vomiting
General disorders and Administration site conditions	Uncommon: pyrexia
Skin and subcutaneous tissue disorders	Not known: rash

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Overdose symptoms have been characterised as a sympathomimetic reaction: tachycardia, profuse sweating, increased bronchial secretion, increased body temperature and restlessness.

There is no known antidote for carglumic acid. The treatment of carglumic acid overdose should consist of general supportive measures.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Amino acids and derivatives; ATC code: A16AA05

Mechanism of action

Carglumic acid is a structural analogue of N-acetylglutamate, which is the naturally occurring activator of

carbamoyl phosphate synthetase, the first enzyme of the urea cycle.

Carglumic acid has been shown *in vitro* to activate liver carbamoyl phosphate synthetase. Despite a lower affinity of carbamoyl phosphate synthetase for carglumic acid than for N-acetylglutamate, carglumic acid has been shown *in vivo* to stimulate carbamoyl phosphate synthetase and to be much more effective than N-acetylglutamate in protecting against ammonia intoxication in rats.

This could be explained by the following observations:

i. The mitochondrial membrane is more readily permeable for carglumic acid than for N-acetylglutamate.
ii. Carglumic acid is more resistant than N-acetylglutamate to hydrolysis by aminoacylase present in the cytosol.

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.

Clinical efficacy and safety

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

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.

5.2 Pharmacokinetic properties

The pharmacokinetics of carglumic acid has been studied in healthy male volunteers using both

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 carglumic acid tablets, plasma concentration peaked at 2,6 µg/ml (median; range 1,8 – 4,8) after 3 hours (median; range 2 – 4).

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).

Diffusion into erythrocytes is non-existent. Protein binding has not been determined.

Biotransformation

A proportion of carglumic acid is metabolised. It is suggested that depending on its activity, the intestinal bacterial flora may contribute to the initiation of the degradation process, thus leading to a variable extent of metabolism of the molecule.

One metabolite that has been identified in the faeces is glutamic acid. Metabolites are detectable in plasma with a peak at 36 – 48 hours and a very slow decline (half-life around 100 hours).

The 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). Their range was consistent with those

measured in healthy adults, even in newborn infants. Whatever the daily dose, they were slowly declining over 15 hours to levels around 100 ng/ml.

Special Populations

Patients with Renal Impairment

The pharmacokinetics of carglumic acid in subjects with renal impairment were compared with subjects with normal renal function following oral administration of a single dose of carglumic acid 40 mg/kg or 80 mg/kg. The C_{max} and AUC_{0-T} of carglumic acid are summarized in the table below. The geometric mean ratio (90 % CI) of AUC_{0-T} in subjects with mild, moderate, and severe renal impairment relative to those in their matched control subjects with normal renal function were approximately 1,8 (1,34, 2,47), 2,8 (2,17, 3,65), and 6,9 (4,79, 9,96), respectively. Renal clearance (CLr) decreased by 0,79-, 0,53-, and 0,15-fold in mild, moderate and severe renal impaired subjects, respectively, when compared to subjects with normal renal function. It is considered that the PK changes of carglumic acid accompanied with impaired renal function are clinically relevant, and dosage adjustment on the dose is warranted in moderate and severe renal impaired subjects [see Posology and method of administration (4.2)].

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Croscarmellose sodium

Hypromellose

Microcrystalline cellulose

Silica colloidal anhydrous

Sodium laurylsulfate

Sodium stearyl fumarate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

After first opening of the tablet container: 3 months.

6.4 Special precautions for storage

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

After first opening of the tablet container:

Do not refrigerate.

Store at or below 30 °C for not longer than three months.

Keep the container tightly closed in order to protect from moisture.

6.5 Nature and contents of container

A 30 ml white round high density polyethylene container suitable for 5 and 15 tablets, with a white round 35 mm polypropylene child-resistant tamper-evident screw cap with a mounted desiccant (silica gel).

A 75 ml white round high density polyethylene container suitable for 60 tablets, with a white round 45 mm polypropylene child-resistant tamper-evident screw cap with integrated desiccant (silica gel).

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Equity Pharmaceuticals (Pty) Ltd.

100 Sovereign Drive

Route 21 Corporate Park

Nellmapius Drive

Irene, Pretoria

South Africa

Tel nr.: + 27 (0) 12 345 1747

8. REGISTRATION NUMBER

52/23/9008

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30 June 2020

10. DATE OF REVISION OF THE TEXT

29 September 2025