NEW ZEALAND DATA SHEET

1 PRODUCT NAME

Carglumic Acid Waymade
200 mg Dispersible Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Each tablet contains 200 mg of carglumic acid.

2.2 Qualitative and quantitative composition

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Dispersible tablet.

The tablets are white to off-white, elongated dispersible tablets with three score marks on both sides and engraved 'N's on one side. Tablets are 18mm long and 6mm wide.

The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Carglumic Acid 200 mg Dispersible Tablets are indicated in the 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 Dose and method of administration

Carglumic acid 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 haemodialysis, 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.

Carglumic acid tablets should not be swallowed whole or crushed. Disperse carglumic acid tablets in water immediately before use. Carglumic acid 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 carglumic acid 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 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 Carglumic Acid 200 mg dispersible tablets.
- 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 (see section 4.4).

<u>Method of administration:</u>
Oral Administration in Adults
Carglumic acid tablets should not be swallowed whole or crushed. Disperse carglumic acid 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. Carglumic acid 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, carglumic acid 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, 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.

Nasogastric Tube Administration in Paediatrics
For patients who have a nasogastric tube in place, 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 and administer immediately through a nasogastric tube. Discard the unused portion.
- Flush with additional water to clear the nasogastric tube.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.
Breast-feeding during the use of carglumic acid is contraindicated (see 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.
This medicinal product contains up to 3 mg sodium per dose, equivalent to 0.15 % of the WHO recommended maximum daily intake for sodium.
The maximum daily dose of this product is equivalent to 20% of the WHO recommended maximum daily intake for sodium.
Carglumic Acid 200 mg Dispersible Tablets are considered high in sodium. This should be particularly taken into account for those on a low salt diet.

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

For carglumic acid no clinical data on exposed pregnancies are available.
Animal studies have revealed minimal developmental toxicity (see section 5.3). Caution should be exercised when prescribing to pregnant women.

Breast-feeding

Although it is not known whether carglumic acid is secreted into human milk, it has been shown to be present in the milk of lactating rats (see section 5.3). Therefore, breast-feeding during the use of carglumic acid is contraindicated. (see section 4.3).

Fertility

No human data on the effect of carglumic acid on fertility are available. In rats, no adverse effects have been observed on male or female fertility with carglumic acid treatment (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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) and uncommon (≥1/1,000 to <1/100). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Undesirable effects in N-acetylglutamate synthase 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 1 Adverse Events reported in ≥ 2 patients treated with carglumic acid 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)

Undesirable effects in organic acidaemia
The most common adverse events, regardless of causality, are anaemia, and thrombocytopenia.

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

Table 2 Adverse Events reported in ≥ 2 patients treated with carglumic acid 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)

For spontaneous cases, the most common adverse events are vomiting, diarrhoea and 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 professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

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 200 mg dispersible 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.

Metabolism

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.

5.3 Preclinical safety data

Safety pharmacology studies have shown that carglumic acid administered orally at doses of 250, 500, 1000 mg/kg had no statistically significant effect on respiration, central nervous system and cardiovascular system.

Carglumic acid showed no significant mutagenic activity in a battery of genotoxicity tests performed in vitro (Ames test, human lymphocyte metaphase analysis) and in vivo (micronucleus test in rat).

Single doses of carglumic acid up to 2800 mg/kg orally and 239 mg/kg intravenously did not induce any mortality or abnormal clinical signs in adult rats. In newborn rats receiving daily carglumic acid by oral gavage for 18 days as well as in young rats receiving daily carglumic acid for 26 weeks, the No Observed 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.

No adverse effects have been observed on male or female fertility. In rats and rabbits no evidence has been seen of embryotoxicity, foetotoxicity or teratogenicity up to maternotoxic doses leading to fifty times exposure as compared to humans in rats and seven times in rabbits. Carglumic acid is secreted in the milk of lactating rats and although developmental parameters were unaffected, there were some effects on body weight / body weight gain of pups breast-fed by dams treated with 500 mg/kg/day and a higher mortality of pups from dams treated with 2000 mg/kg/day, a dose that caused maternotoxicity. The maternal systemic exposures after 500 and 2000 mg/kg/day were twenty five times and seventy times the expected human exposure.

No carcinogenicity study has been conducted with carglumic acid.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Croscarmellose sodium
Sodium laurilsulfate
Silica colloidal anhydrous
Sodium stearyl fumarate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months when stored at or below 30 °C.
After first opening of the tablet container: 1 month

6.4 Special precautions for storage

Store at or below 25°C.
After first opening of the tablet container: Do not refrigerate or freeze.
Keep the container tightly closed in order to protect from moisture.

6.5 Nature and contents of container

5, 15 or 60 tablets in a high density polyethylene container with a child resistant polypropylene cap with a liner and a desiccant unit.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements

7 MEDICINE SCHEDULE

Prescription Only Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

1 October 2020

10 DATE OF REVISION OF THE TEXT

SUMMARY TABLE OF CHANGES