

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Carglumic Acid Waymade 200 mg Dispersible Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 mg of carginic acid.

Excipient(s) with known effect

Each tablet contains up to 3 mg of sodium (see section 4.4).

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, 18 mm x 6 mm, with three score marks on both sides and engraved 'N's on one side.

The tablet can be divided into equal doses.

4.1 Therapeutic indications

Carginic 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 Posology and method of administration

Carginic Acid 200 mg Dispersible Tablet treatment should be initiated under the supervision of a physician 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 (see 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 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).

Renal impairment:

Caution is advised when administering Carglumic Acid 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 hyperammonemia 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 \leq 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 Carglumic Acid for the treatment of pediatric patients (birth to 17 years of age) with acute or chronic hyperammonemia due to NAGS deficiency and acute hyperammonemia due to IVA, PA or MMA have been established, and based on these data, posology adjustments in neonates are not deemed necessary.

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 physician. 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.

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 tablet, 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.

Use in patients with renal impairment

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

4.5 Interaction with other medicinal products and other forms of interaction

No 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 ($\geq 1/10$), common ($\geq 1/100$ to $<1/10$) and uncommon ($\geq 1/1,000$ to $<1/100$).

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

- Undesirable effects in N-acetylglutamate synthase deficiency

Investigations	<i>Uncommon</i> : increased transaminases
Skin and subcutaneous tissue disorders	<i>Common</i> : increased sweating <i>Not known</i> : rash

- Undesirable effects in organic acidaemia

Cardiac disorders	<i>Uncommon</i> : bradycardia
Gastrointestinal disorders	<i>Uncommon</i> : 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 medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google play or Apple App Store.

4.9 Overdose

In one patient treated with carginic 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.

5.1 Pharmacodynamic properties

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

Mechanism of action

Carginic 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.

Carginic acid has been shown in vitro to activate liver carbamoyl phosphate synthetase. Despite a lower affinity of carbamoyl phosphate synthetase for carginic acid than for N-acetylglutamate, carginic 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 carginic acid than for N-acetylglutamate
- ii) Carginic 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). Carginic 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, carginic 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.

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 (CL_r) 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 would be warranted in moderate and severe renal impaired subjects [see Posology and method of administration (4.2)].

Mean (\pm SD) C_{\max} and AUC_{0-T} of Carglumic Acid Following Single Oral Dose Administration of carglumic acid 80 mg/kg or 40 mg/kg in Subjects with Renal Impairment and Matched Control Subjects with Normal Renal Function

PK parameters	Normal Function (Ia) N=8	Mild Impairment N=7	Moderate Impairment N=6	Normal Function (Ib) N=8	Severe Impairment N=6
	80 mg/kg			40 mg/kg	
C_{\max} (ng/ml)	2982.9 (552.1)	5056.1 (2074.7)	6018.8 (2041.0)	1890.4 (900.6)	8841.8 (4307.3)
AUC_{0-T} (ng [*] h/ml)	28312.7 (6204.1)	53559.3 (20267.2)	80543.3 (22587.6)	20212.0 (6185.7)	144924.6 (65576.0)

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

Bottle

3 years
After first opening of the tablet container: 1 month

Blister

3 years

6.4 Special precautions for storage

Bottle

This medicinal product does not require any special storage conditions.
After first opening of the tablet container: do not refrigerate or freeze.
Keep the container tightly closed in order to protect from moisture.

Blister

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Bottle

5, 15 or 60 tablets in a high density polyethylene container with a child resistant polypropylene cap with a liner and a desiccant unit.

Blister

5, 15 or 60 tablets in an Alu/Alu blister.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Waymade Plc trading as Sovereign Medical
Sovereign House
Miles Gray Road
Basildon
Essex
SS14 3FR
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 06464/3072

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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