NEW ZEALAND DATA SHEET

UCEDANE carglumic acid tablets

1. PRODUCT NAME

Ucedane 200 mg dispersible tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 mg of carglumic acid. For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersible tablet.

The tablets are rod-shaped, white and biconvex with three score lines on both sides and engraving "L/L/L/L" on one side.

The tablet can be divided into four equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ucedane is indicated in treatment of hyperammonaemia due to N-acetylglutamate synthase primary deficiency.

4.2 Dose and method of administration

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

Posology

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 Ucedane.
- 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.

Method of administration

This medicine is for oral use ONLY (ingestion or via 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 intakes 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.

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.

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

None

4.5 Interaction with other medicinal products 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).

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) 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.

System Organ Class	Frequency	Adverse reaction
Cardiac disorders	Uncommon	bradycardia
Gastrointestinal disorders	Uncommon	diarrhea, vomiting
Skin and subcutaneous tissue disorders	Common	increased sweating
	Not known	rash
General disorders and Administration site	Uncommon	pyrexia
Investigations	Uncommon	increased transaminases

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

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

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.

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.

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.

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
mannitol
colloidal anhydrous silica
sodium stearyl fumarate
crospovidone type B
copovidone K 28.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Blister (ALU/ALU) packed in cartons. Pack size of 12 or 60 dispersible tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Orpharma NZ Limited
c/o Staples Rodway Limited
Level 9, 45 Queen Street
P O Box 3899
Auckland 1140

9. DATE OF FIRST APPROVAL

12 August 2021

10. DATE OF REVISION OF THE TEXT

SUMMARY TABLE OF CHANGES

Date of Revision	Section Changed	Summary of new information
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