

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Carbaglu 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 a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Dispersible tablet

The tablets are white and elongated with three score marks and engraved on one side.

The tablet can be divided into equal halves.

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 methymalonic acidaemia.
- hyperammonaemia due to propionic acidaemia.

4.2 Posology and method of administration

Carbaglu 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 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 (see section 4.4).

Method of administration:

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.

Breast-feeding during the use of carginic 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 carginic 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.

4.5 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 carginic 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.

Breastfeeding

Although it is not known whether carginic 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 carginic 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 ($\geq 1/10$), 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

- Undesirable effects in organic acidaemia

Cardiac disorders	<i>Uncommon</i> : bradycardia
Gastrointestinal disorders	<i>Uncommon</i> : diarrhoea, vomiting
General disorders and Administration site conditions	<i>Uncommon</i> : pyrexia

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.

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:

- The mitochondrial membrane is more readily permeable for carglumic acid than for N-acetylglutamate
- 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 Carbaglu 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 Carbaglu administered orally at doses of 250, 500, 1000 mg/kg had no statistically significant effect on respiration, central nervous system and cardiovascular system.

Carbaglu 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
sodium laurilsulfate
hypromellose
croscarmellose sodium
silica colloidal anhydrous
sodium stearyl fumarate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months
After first opening of the tablet container: 1 month

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C)

After first opening of the tablet container:
Do not refrigerate.
Do not store above 30°C.
Keep the container tightly closed in order to protect from moisture.

6.5 Nature and contents of container

5-, 15- or 60- polypropylene tablet containers closed by a polyethylene cap with a desiccant unit.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

Orphan Europe SARL
Immeuble “Le Wilson”
70 avenue du Général de Gaulle
F-92800 Puteaux
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/246/001 (15 dispersible tablets)

EU/1/02/246/002 (60 dispersible tablets)

EU/1/02/246/003 (5 dispersible tablets)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24 January 2003

Date of renewal: 24 January 2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMA) <http://www.ema.europa.eu/>.

ANNEX II

- A. MANUFACTURING AUTHORISATION HOLDER
RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OF THE MARKETING AUTHORISATION**

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Orphan Europe SARL, Immeuble 'Le Wilson', 70 avenue du Général de Gaulle, F-92800 Puteaux, France

B. CONDITIONS OF THE MARKETING AUTHORISATION

• **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2)

• **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

• **OTHER CONDITIONS**

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the Marketing Authorisation, is in place and functioning before and whilst the product is on the market.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON BOX AND TABLET CONTAINER LABEL X 5 TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Carbaglu 200 mg dispersible tablets
Carglumic acid

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 200 mg of carglumic acid.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

5 dispersible tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}
Discard one month after first opening.
Opened:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C)

After first opening of the tablet container: do not refrigerate, do not store above 30°C.
Keep the container tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

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France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/246/003

13. BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

Carbaglu 200 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON BOX AND TABLET CONTAINER LABEL X 15 TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Carbaglu 200 mg dispersible tablets
Carglumic acid

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 200 mg of carginic acid.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

15 dispersible tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}
Discard one month after first opening.
Opened:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C)

After first opening of the tablet container: do not refrigerate, do not store above 30°C.
Keep the container tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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EU/1/02/246/001

13. BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Carbaglu 200 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON BOX AND TABLET CONTAINER LABEL X 60 TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Carbaglu 200 mg dispersible tablets
Carglumic acid

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 200 mg of carginic acid.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 dispersible tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}
Discard one month after first opening.
Opened:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C)

After first opening of the tablet container: do not refrigerate, do not store above 30°C.
Keep the container tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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12. MARKETING AUTHORISATION NUMBER(S)

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13. BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Carbaglu 200 mg

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Carbaglu 200 mg dispesible tablets Carglumic acid

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist

In this leaflet:

1. What Carbaglu is and what it is used for
2. Before you take Carbaglu
3. How to take Carbaglu
4. Possible side effects
5. How to store Carbaglu
6. Further information

1. WHAT CARBAGLU IS AND WHAT IT IS USED FOR

Carbaglu can help eliminating excessive ammonia plasma levels (elevated ammonia level in the blood). Ammonia is especially toxic for the brain and leads, in severe cases, to reduced levels of consciousness and to coma.

Hyperammonaemia may be due to

- the lack of a specific liver enzyme N- acetylglutamate synthase. Patients with this rare disorder are not able to eliminate nitrogen waste, which builds up after eating protein. . This disorder persists during the entire life of the affected patient and therefore the need for this treatment is lifelong.
- isovaleric acidaemia, methylmalonic acidaemia or propionic acidaemia. Patients suffering from one of these disorders need treatment during the hyperammonaemia crisis.

2. BEFORE YOU TAKE CARBAGLU

Do not take Carbaglu:

Do not take Carbaglu if you are hypersensitive (allergic) to carginic acid or any of the other ingredients of Carbaglu.

Do not take Carbaglu during breast-feeding

Take special care with Carbaglu:

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

Your doctor will evaluate your individual responsiveness to carginic acid before initiating any long term treatment.

The dose should be individually adjusted in order to maintain normal ammonia plasma levels.

Your doctor may prescribe supplemental arginine or restrict your protein intake.

In order to follow-up your condition and your treatment, your doctor may examine your liver, your kidneys, your heart and your blood on a regular basis.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription

Taking Carbaglu with food and drink

Carbaglu must be taken orally before meals or feedings.

The tablets must be dispersed in a minimum of 5 to 10 ml of water and taken immediately. The suspension has a slightly acidic taste.

Pregnancy and Breast-feeding

The effects of Carbaglu on pregnancy and the unborn child are not known. Please consult your doctor for advice if you are pregnant or planning to become pregnant.

The excretion of carginic acid into breast milk has not been studied in women. Nevertheless, as carginic acid has been shown to be present in the milk of lactating rats with potential toxic effects for their fed pups, you should not breast feed your baby if you are taking Carbaglu.

Driving and using machines

Effects on the ability to drive and use machines are not known.

3. HOW TO TAKE CARBAGLU

Always take Carbaglu exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.

The usual dose:

the initial daily dose is usually 100 mg per kilogram of body weight, up to a maximum of 250 mg per kilogram of body weight (for example, if you weight 10kg, you should take 1g per day, or 5 tablets), For patients suffering from N-acetylglutamate synthase deficiency, in the long term, the daily dose usually ranges from 10 mg to 100 mg per kilogram of body weight.

Your doctor will determine the dose suitable to you in order to maintain normal ammonia levels in your blood.

When the patient is in hyperammonaemic coma, Carbaglu is administered by fast push through a syringe via the tube set up and used to feed you..

If you take more Carbaglu than you should:

Ask your doctor or pharmacist for advice.

If you forget to take Carbaglu:

Do not take a double dose to make up for forgotten individual doses.

If you stop taking Carbaglu

Do not stop Carbaglu without informing your doctor.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Carbaglu can have side effects, although not everybody gets them.

The following side effects were reported as follows: very common (occurring in at least one in 10 patients), common (occurring in at least one in 100 patients), uncommon (occurring in at least one

in 1,000 patients), rare (occurring in at least one in 10,000 patients), very rare (occurring in at least one in 100,000 patients).

- *Common*: increased sweating
- *Uncommon*: bradycardia (decreased frequency of the heart), diarrhoea, fever, increased transaminases, vomiting

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE CARBAGLU

Keep out of the reach and sight of children.

Do not use after the expiry date stated on the tablet container.

Store in a refrigerator (2°C – 8°C)

After first opening of the container: do not refrigerate, do not store above 30°C.

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

Write the date of opening on the tablet container. Discard 1 month after first opening.

6. FURTHER INFORMATION

What Carbaglu contains

- The active substance is carglumic acid. Each tablet contains 200 mg of carglumic acid.
- The other ingredients are microcrystalline cellulose, sodium laurilsulfate, hypromellose, croscarmellose sodium, silica colloidal anhydrous, sodium stearyl fumarate.

What Carbaglu looks like and contents of the pack

Carbaglu 200mg tablet is a bar-shaped tablet, with 4 punches on one side with 3 break-mark sides.

Carbaglu is presented in container of 5, 15 and 60 tablets

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This leaflet was last approved on

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>. There are also links to other websites about rare diseases and treatments.