Date: 10 September 2020
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Carbaglu

International non-proprietary name: acidum carglumicum
Pharmaceutical form: dispersible tablet for ingestion
Dosage strength: 200 mg
Route(s) of administration: oral
Marketing Authorisation Holder: RECORDATI AG
Marketing Authorisation No.: 67376
Decision and Decision date: approved on 28 July 2020

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
Cmax	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
ERA	Environmental Risk Assessment
GLP	Good Laboratory Practice
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
N/A	Not applicable
NAGS	N-acetylglutamate synthase primary deficiency
NO(A)EL	No Observed (Adverse) Effect Level
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PSP	Pediatric Study Plan (US-FDA)
RMP	Risk Management Plan
SwissPAR	Swiss Public Assessment Report
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance, carglumic acid, of the medicinal product mentioned above.

Orphan drug status
The applicant requested Orphan Drug Status in accordance with Article 4 a^{decies} no. 2 of the TPA. The Orphan Status was granted on 8 March 2019.

2.2 Indication and Dosage

2.2.1 Requested Indication

Carbaglu is indicated for the treatment of
- Hyperammonaemia due to a primary deficiency of N-acetylglutamate synthase
- Hyperammonaemia due to isovaleric acidaemia
- Hyperammonaemia due to methylmalonic acidaemia
- Hyperammonaemia due to propionic acidaemia

2.2.2 Approved Indication

Carbaglu is indicated for the 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.

2.2.3 Requested Dosage

The treatment using Carbaglu should be initiated under supervision of a doctor experienced in the treatment of metabolism disorders.

Dosage in the treatment of N-acetylglutamate synthase deficiency:
The treatment can already be initiated on the first day of life based on clinical experience. The initial daily dosage should be 100 mg/kg, up to 250 mg/kg if necessary. The dosage should be adjusted individually in order to maintain normal ammonia plasma levels (see "Warnings and precautions"). In the long term it may not be necessary to increase the dosage according to body weight as long as adequate metabolic control is achieved. The daily dosage range from 10 mg/kg to 100 mg/kg.

Carglumic acid responsiveness test
It is recommended to test the responsiveness to carglumic acid in every single patient before initiating the treatment.
- In a comatose child, the initial dosage should be 100 to 250 mg/kg/day. The concentration of ammonia in plasma should be measured at least before each administration. The concentration of ammonia should normalise within a few hours after starting Carbaglu.
- In a patient with moderate hyperammonaemia, a test dose of 100 to 200 mg/kg/day should be administered for 3 days with a constant protein intake. Repeated determinations of ammonia plasma concentration should be performed (1 hour before and 1 hour after a meal) and the dosage should be adjusted in order to keep a normal ammonia in plasma levels.

For isovaleric acidaemia, methylmalonic acidaemia and propionic acidaemia:
In patients with organic acidaemia, the treatment should be started upon hyperammonaemia. The initial daily dosage should be 100 mg/kg, up to 250 mg/kg if necessary. After the initial treatment, the

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dosage should be individually adjusted in order to maintain normal ammonia plasma levels (see “Warnings and precautions”).

Infants and adolescents
See above.

Mode of administration
This drug is exclusively for oral administration (swallowing or via a nasogastric tube using a syringe). Based on pharmacokinetic data and clinical experience, it is recommended to divide the total daily dose into 2 to 4 doses to be given before meals or feedings. The division of the tablet into halves enables most of the required posology adjustments. In some cases, the use of a quarter tablet is reasonable to adjust the posology prescribed by the doctor.
The tablets must be dispersed in a minimum of 5 to 10 ml of water and immediately administered (swallowed or quickly administered through a syringe via a nasogastric tube).
The suspension has a slightly acidic taste.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	22 January 2019
Formal control completed	12 February 2020
List of Questions (LoQ)	10 June 2019
Answers to LoQ	5 December 2019
Predecision	3 March 2020
Answers to Predecision	30 April 2020
Final Decision	28 July 2020
Decision	approval

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3 Medical Context

Liver enzyme N-acetylglutamate synthase (NAGS) deficiency is a very rare disease causing high plasma levels of ammonia. The deficiency causes damage to the central nervous system, leading to cerebral oedema, coma and eventually death. Symptoms are usually visible within the first week of life. Early diagnosis and treatment are essential to decelerate the progression of neurological damage.

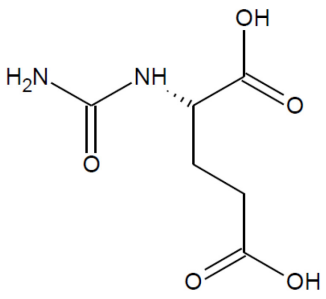
4 Quality Aspects

4.1 Drug Substance

Drug substance

INN:	Carglumic acid
Chemical names:	N–carbamoyl-L-glutamic acid; (2S)-2-(carbamoylamino) pentanedioic acid
Molecular formula:	$C_6H_{10}N_2O_5$
Molecular mass:	190.16 g/mol

Molecular structure:



Physico-chemical properties: Carglumic acid is a white crystalline powder. It has one asymmetric centre and is manufactured as the S-isomer. Carglumic acid is manufactured in one crystalline form. The solubility of carglumic acid is pH dependent.

Synthesis: The synthesis of the drug substance has been adequately described, and the process is controlled with appropriate in-process controls and tests for isolated intermediates.

Structure elucidation: The structure of carglumic acid has been fully elucidated using several spectroscopic techniques.

Specifications: The active substance specifications include tests for appearance, identification, specific optical rotation (Ph. Eur.), loss on drying (Ph. Eur.), residue on ignition (Ph. Eur.), pH of a solution (Ph. Eur.), heavy metals (Ph. Eur.), melting point (Ph. Eur.), assay (HPLC) and related substances (HPLC). The specifications conform to the requirements outlined in ICH guideline Q6A and are considered appropriate in order to ensure a consistent drug substance quality.

Stability: The bulk drug substance is packaged in two LDPE bags. A desiccant bag is placed between the internal and external LDPE bags. The closed LDPE bags are placed in a secondary HDPE container. Appropriate stability data have been generated, resulting in a suitable retest period when packaged in the packaging type described above.

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4.2 Drug Product

Description and composition: Carbaglu dispersible tablets are presented as immediate-release tablets containing 200 mg of carglumic acid as active substance. The dispersible tablets are white, bar-shaped tablets, scored with three break-marks on both sides and engraved on one side (“c c c c”). The dimensions are 18.0 x 6.0 mm. The tablets are easily dispersible in water with a rapid in vitro dissolution profile. The dispersible tablets consist of the pharmaceutical excipients microcrystalline cellulose, sodium laurilsulfate, hypromellose, croscarmellose sodium, sodium stearyl fumarate and silica colloidal anhydrous. Because the dose is adapted to individual requirements, scored tablets have been chosen, as they provide dose regimen flexibility through the breaking of the tablets into halves or quarters. The breakability of the tablet into halves or quarters has been demonstrated.

Manufacture: Carbaglu dispersible tablets are manufactured by a standard manufacturing process that includes wet granulation, drying, milling, blending, and compression. Process parameters and in-process controls are defined in order to ensure consistent tablet quality. Validation was performed on production-scale batches.

Specification: For the control of the finished product, adequate tests and acceptance criteria for release and at shelf-life are established. The specifications include the parameters appearance, uniformity of mass (Ph. Eur.), disintegration time (Ph. Eur.), fineness of the dispersion (Ph. Eur.), identification tests, assay (HPLC), degradation products (HPLC), dissolution, and microbial purity. The corresponding analytical test procedures have been adequately validated.

Container-Closure System: Carbaglu dispersible tablets are packaged in a high-density polyethylene tablet container closed by a child-resistant polypropylene screw cap with a desiccant unit.

Stability: Drug product stability studies were conducted with various batches. Appropriate stability data have been generated in the packaging material for commercial use and following the relevant international guidelines. Based on these studies, an appropriate shelf-life was established for the dispersible tablets. The storage recommendation for the unopened commercially packaged product is “Store in a refrigerator (2-8°C)”.

In-use-stability: The results from a complementary stability study support the recommended shelf life of 3 months after first opening of the tablet container. The storage recommendations are: “Store below 30°C. Do not refrigerate. Keep the container tightly closed in order to protect from moisture”.

4.3 Quality Conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

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5 Nonclinical Aspects

Regarding the marketing authorisation application for Carbaglu, Swissmedic Preclinical Review conducted an abridged evaluation that was based on the assessment reports from EMA, FDA, and TGA. Post-marketing studies, including a carcinogenicity study in rats and *in vitro* studies on drug interaction potential, were reviewed.

Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Carbaglu in the proposed indication. The pharmaco-toxicological profile has been sufficiently characterised, and all relevant nonclinical data are mentioned in the information for healthcare professionals. Although no particular safety issues were identified in single-dose studies and chronic repeated-dose studies in rats, there were dose-related adverse findings in heart and kidneys (myxomatous changes of the valves, valvular thrombosis, and associated renal infarcts) at all doses (≥100 mg/kg/day) in the 2-year carcinogenicity study. There is no adequate safety margin, and the clinical relevance of these findings is unknown. To date, the clinical data (including the post-marketing surveillance data) do not indicate a particular risk for humans. However, the renal and cardiac function of patients on carglumic acid treatment should be systematically monitored. This is adequately stated in the information for healthcare professionals.

The summary of the findings of the nonclinical safety studies in the RMP is generally acceptable. However, the adverse effects on heart and kidneys observed in the rat carcinogenicity study should also be described; this was requested as a post-approval commitment.

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6 Clinical and Clinical Pharmacology Aspects

The available assessment reports and respective product informations from EMA and FDA were used as a basis for the clinical and clinical pharmacology evaluation. For further details concerning the efficacy, safety and clinical pharmacology see Chapter 8.1 of this report.

6.1 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

8.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Carbaglu was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

CARBAGLU®

Composition

Active substances

Carglumic acid.

Excipients

Microcrystalline cellulose, sodium lauryl sulphate, hypromellose, croscarmellose sodium, highly dispersed silica, and sodium stearyl fumarate. One tablet contains 1.66 mg of sodium.

Pharmaceutical form and active substance quantity per unit

Dispersible tablet for ingestion.
Each tablet contains 200 mg of carglumic acid.
White, oblong tablets with three score marks and engraved on one side.
The tablets can be divided into equal halves.

Indications/Applications

Carbaglu is indicated for the 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.

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 on 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 plasma ammonia plasma levels (see “Warnings and precautions”).

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 dose range is 10 mg/kg up 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 "Warnings and precautions").

Children and adolescents

See above.

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.

Contraindications

Hypersensitivity to the active substance or to any of the excipients.
Breastfeeding is contraindicated during the use of carglumic acid (see "Pregnancy, breastfeeding" and "Preclinical data").

Warnings and precautions

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 less than 1 mmol sodium (23 mg) per dose (i.e. it is almost sodium-free).

Interactions

No clinical interaction studies have been performed.

Based on in vitro studies, Carbaglu does not induce the enzymes CYP1A1/2, CYP2B6, CYP2C, and CYP3A4/5 and does not inhibit the enzymes CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5.

Carglumic acid is a substrate of OAT1. A clinical relevance is not excluded.

In *in vitro* studies, carglumic acid was not an inhibitor of the transporters BCRP, BSEP, MATE1, MATE2-K, MDR1, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, and OCT2.

Pregnancy, lactation

Pregnancy

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

Animal studies have revealed minimal developmental toxicity (see “Preclinical data”). 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 “Preclinical data”). Therefore, breast-feeding during the use of carglumic acid is contraindicated (see “Contraindications”).

Effect on ability to drive and use machines

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

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), 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 for 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
The reporting of suspected adverse reactions after authorisation is very important. It allows continued monitoring of the risk-benefit balance of the medicinal product. Healthcare professionals are asked to report any suspected new or serious adverse reactions via the ElViS (Electronic Vigilance System) online portal. You can find more information at www.swissmedic.ch.

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.

Properties/Effects

ATC-Code

A16A A05
Pharmacotherapeutic group: Amino acids and derivatives

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.

Pharmacodynamics

Other studies conducted in rats under different experimental conditions (starvation, protein-free diet, or high-protein diet) leading to increased ammonia availability. Carglumic acid was shown to decrease blood ammonia levels and increase urea levels in blood and urine, whereas the level of carbamoyl phosphate synthetase activators in the liver was significantly increased.

Clinical efficacy

In patients with N-acetyglutamate synthase deficiency, carglumic acid was shown to induce a rapid normalization of plasma ammonia levels, usually within 24 hours.
When the treatment was initiated before any permanent brain damage, the 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.

Pharmacokinetics

The pharmacokinetics of carglumic acid has been studied in healthy male volunteers using both radiolabelled and unlabelled product.

Absorption

The median Tmax value of Carbaglu was 3 hours (range: 2–4). The absolute bioavailability was not determined.

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 nonexistent. Protein binding has not been determined.

Metabolism

It is suggested that a part of the carglumic acid is metabolised by the intestinal bacterial flora. One metabolite identified in faeces is glutamic acid. Metabolites are detectable in plasma with a maximum at 36-48 hours and a very slow decline (half-life about 100 hours).
The likely end product of the carglumic acid metabolism is carbon dioxide, which is eliminated through the lungs.

Elimination

After taking a single dose of 100 mg/kg body weight, 9% of the dose is excreted unchanged in the urine and up to 60% in the faeces.

Kinetics of special patient groups

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.

Preclinical data

Safety pharmacology

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

Single and repeated dose toxicity

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 an 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 determined at 500 mg/kg/day and the No Observed Adverse Effect Level (NOAEL) was established at 1000 mg/kg/day (exposure (AUC) approx. 15 times the human exposure after single administration of 100 mg/kg).
In the two-year carcinogenicity study, rats treated with carglumic acid showed increased myxomatous changes in the heart valves (especially mitral valve), valve thrombosis, and renal infarction from the lowest dose (100 mg/kg/day). The clinical relevance of these findings is unknown.

Genotoxicity

Carbaglu showed no significant mutagenic activity in a number of genotoxicity tests performed *in vitro* (Ames test, human lymphocyte metaphase analysis) and *in vivo* (micronucleus test in rats).

Carcinogenicity

In a two-year carcinogenicity study in rats at doses up to 1000 mg/kg/day, carglumic acid showed no carcinogenic potential.

Reproductive toxicity

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 70 times exposure as compared to humans in rats and 6 times in rabbits after single administration of 100 mg/kg. 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 23 times resp. 70 times the expected human exposure after single administration of 100 mg/kg.

Other information

Incompatibilities

Not applicable.

Shelf life

The medicinal product may only be used up to the date indicated on the package after “EXP”.

Shelf life after opening

After first opening of the tablet container: 3 months shelf life.

Special precautions for storage

Store in a refrigerator (2–8°C) in the original packaging.
After first opening of the bottle: Do not refrigerate. Do not store above 30°C.
Keep the bottle tightly closed in order to protect the content from moisture.
Keep out of the reach of children.

Authorisation number

67376 (Swissmedic).

Packages

Packages of 5 and 60 tablets (divisible) (B).

Marketing authorisation holder

Recordati AG, 6340 Baar.

Date of revision of the text

July 2020