PART VI: Summary of the risk management plan by product

Active substance	*carglumic acid*
Product(s) concerned (brand name(s)):	CARBAGLU®
MAH/Applicant name	Recordati Rare Diseases

Data lock point for this module: 27 July 2022

Version number of RMP when this module was last updated : Version number: 6.0

QPPV name: Anne Valot-Salengro, MD

QPPV signature:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of "Carbaglu" is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of "Carbaglu" in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. "Recordati AG" is fully responsible for the accuracy and correctness of the content of the published summary RMP of "Carbaglu"

VI.1 Elements for summary tables in the EPAR

VI.1.1 *Summary table of Safety concerns*

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	Use in pregnant women Patients with cardiac diseases/renal and hepatic impairment Long term safety

VI.1.2 *Table of on-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan*

Study title **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances.				
Not applicable				
Category 3 - Required additional pharmacovigilance activities **(Food and Drug Administration requirement)**				
Study 1604-2: A registry of patients, including infants with NAGS deficiency and treated with CGA to obtain long-term clinical safety information. Ongoing	To obtain long-term clinical safety information in patients with NAGS deficiency treated with CGA.	Assess treatment with CGA for: - Use in pregnant women - Patients with cardiac diseases/renal and hepatic impairment -Long-term safety	Study start	Apr 2012
			Study completion	January 2027
Study 1604-3: A study of the effects of CGA on pregnancy and foetal outcomes. Ongoing	To study of the effects of CGA on pregnancy and foetal outcomes.	Assess treatment with CGA for Use in pregnant women.	Study start	Apr 2012
			Study completion	January 2027

RRDUS-PASS-0573: Short and long-term effects of the Carbaglu® treatment of hyperammonaemia due to MMA and PA in the adult and paediatric patient population. Ongoing	Obtain short- and long-term clinical safety data in pediatric and adult patients with PA and MMA treated with Carbaglu.	Assess treatment with CGA for: -Long term safety -Use in pregnant women	Study start	June 2022
			Study completion	December 2032
Category Other studies in the pharmacovigilance plan				
PROTECT Study: Understanding the long-term management of organic acidaemia patients with Carbaglu: A mixed methods approach. Ongoing	To describe the number and duration of decompensation events in patients with a diagnosis of MMA or PA who have been receiving Carbaglu for a minimum of 6 months compared to the number and duration of decompensation events that occurred prior to starting treatment with Carbaglu.	Assess treatment with CGA for long-term safety.	Study start	January 2019
			Study completion	September 2026

CGA=carglumic acid; NAGS=N-acetylglutamate synthase.

VI.1.3 Summary of Post authorisation efficacy development plan

No post-authorization efficacy studies are planned or ongoing for Carbaglu.

VI.1.4 *Summary table of Risk Minimisation Measures*

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks - None		
Important potential risks - None		
Missing information		
Use in pregnant women	<u>Routine risk minimisation measures:</u> SmPC Section 4.6. PL section 2. Section 4.6 of the SmPC for CGA which notes that animal studies have revealed minimal developmental toxicity, and that caution should be exercised when prescribing to pregnant women. Section 4.6 of the SmPC for CGA which notes that CGA has been	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> None. <u>Additional pharmacovigilance activities:</u> Study 1604-2 and Study 1604-3 Study RRDUS-PASS-0573

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	shown to be present in the milk of lactating rats; therefore, breast-feeding during the use of CGA is contraindicated. Section 2 of the PL for Carbaglu notes that patients should consult their doctor or pharmacist for advice before taking the medicine in case of pregnancy, pregnancy suspicion or if they are planning to become pregnant. Legal status: Subject to restricted medical prescription. Treatment should be supervised by a physician experienced in the management of metabolic disorders. <u>Additional risk minimisation measures:</u> None.	

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Patients with cardiac diseases/renal and hepatic impairment	<u>Routine risk minimisation measures:</u> SmPC Sections 4.2 and 4.4 PL section 2 and 3. Section 4.2 and 4.4 of the SmPC for Carbaglu note that caution is advised when administering Carbaglu to patients with impaired renal function and that the dose of Carbaglu must be reduced in patients with renal impairment, respectively. Section 4.2 of the SmPC for Carbaglu contains guidance on dose adjustments for patients with renal impairment. Section 3 of the PL advises patients to notify their doctor in case of renal impairment as the daily dose should be reduced. Section 4.4 of the SmPC for CGA which notes that very few data on the safety of CGA are available; therefore, systematic surveillance of liver, renal, cardiac functions and haematological parameters is recommended. Section 2 of the PL notes that regular liver, kidneys, heart and blood monitoring may be planned by the patients' doctors. Legal status: Subject to restricted medical prescription. Treatment should be supervised by a physician experienced in the management of metabolic disorders. <u>Additional risk minimisation measures:</u> None.	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> None. <u>Additional pharmacovigilance activities:</u> Study 1604-2.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Long term safety	Routine risk minimisation measures: None Legal status: Subject to restricted medical prescription. Treatment should be supervised by a physician experienced in the management of metabolic disorders. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: PROTECT study Study RRDUS-PASS-0573 Study 1604-2

CGA=carglumic acid; PL=Package Leaflet; SmPC=Summary of Product Characteristics.

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Hyperammonaemia due to N-acetylglutamate synthase primary deficiency

N-acetylglutamate synthase primary deficiency is the rarest congenital UCD, which results in a severe defect of ammonia detoxification, which is fatal if untreated. When ammonaemia levels reach above 350 μmol/L at the first hyperammonaemic attack, most patients die or have severe neurological damage Therefore, treatment must be started within 24 hours of hyperammonaemia diagnosis (as presumptive diagnosis of NAGS primary deficiency) to avoid irreversible brain damage. The major cause of mortality and morbidity is hyperammonaemia. Most therapeutic interventions have focused on the prevention and treatment of hyperammonaemia. However, as a cohort of treated patients gets older, other complications have appeared even without significant history of recurrent hyperammonaemia. The incidence of urea cycle disorders (UCDs), although difficult to ascertain, is estimated to be 1 in 35 000 living births. N-acetylglutamate synthase primary deficiency is the rarest of these disorders, with an estimated incidence of 1:3 500 000 to 7 000 000.

Hyperammonaemia due to organic acidaemia

Metabolic decompensation in IVA is potentially life threatening and can cause neurological sequelae, resulting in significant morbidity and mortality. A total of 40% of patients with MMA die between 40 days and 3 years; survival from 2 to 8 years is 60%. The outcome for children with severe forms of MMA remains poor. Patients have recurrent episodes of metabolic decompensation; many have neurodevelopmental complications and mortality is high. Long-term survivors develop chronic renal failure. In young patients with early-onset disease, liver transplantation might prevent complications and, for those in end-stage renal failure, kidney transplantation could be combined with that of the liver. The incidence of IVA has a range from 1:62 500 live births in parts of Germany to 1:250 000 in the US. The incidence of MMA in Western populations have ranged from 1:48 000 to 1:61 000 births, and overall incidence is believed to be around 1:50 000. The incidence of PA in Western populations have ranged from 1:50 000 to 1:500 000 births, and overall incidence is believed to be approximately 1:100 000 to 150 000.

VI.2.2 Summary of treatment benefits

Carbaglu has been shown in vitro to activate liver CPS. Despite a lower affinity of CPS for Carbaglu compared to that for NAG, Carbaglu has been shown in vivo to stimulate CPS and to be much more effective than NAG in protecting against ammonia intoxication in rats. This could be explained by the following
observations:

- The mitochondrial membrane is more readily permeable for Carbaglu than for NAG.
- Carbaglu is more resistant than NAG to hydrolysis by aminoacylase present in the cytosol.

Other studies have been conducted in rats under different experimental conditions leading to increased ammonia availability (i.e. starvation, protein-free or high-protein diet) Carbaglu was shown to decrease blood ammonia levels and increase urea levels in bloo and urine, whereas the liver content of CPS activators was significantly increased.

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 exhibite 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.

VI.2.3 Unknowns relating to treatment benefits

There are limited or no information concerning Carbalgu in pregnant and breastfeeding women, and effects on ability to drive and use machines have been performed. Therefore, it is unknown whether use of carbaglu in these populations will be profitable and safe.

VI.2.4 *Summary of safety concerns*

Important identified risks

None

Important potential risks

None

Missing information

Risk	What is known

Limited information on the use of CGA during pregnancy.	Section 4.6 (Fertility, pregnancy and lactation) of the SmPC for CGA states that 'Animal studies have revealed minimal developmental toxicity. Caution should be exercised when prescribing to pregnant women.' The anticipated risk of use during pregnancy is to be further investigated and is considered missing information.
Limited information on the use of CGA in patients with cardiac diseases/renal and hepatic impairment.	Section 4.4 (Special warnings and precautions for use) of the SmPC for Carbaglu notes that the dose of Carbaglu must be reduced in patients with renal impairment. Section 4.2 of the the SmPC for Carbaglu contains guidance on dose adjustments for patients with renal impairment and reminds that caution is advised when administering Carbaglu to patients with impaired renal function. Section 4.4 (Special warnings and precautions for use) of the SmPC for CGA states that 'As very few data on the safety of CGA are available, systematic surveillance of liver, renal, cardiac functions and haematological parameters is recommended.' The anticipated risk of CGA use in this patient population is to be further investigated and is considered missing information.
Limited information on long term safety	The anticipated risk on long term safety is investigated in 3 ongoing Non interventional studies.

CGA=carglumic acid; SmPC=Summary of Product Characteristics; CCDS=Company Core Data Sheet; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term

VI.2.5 *Summary of risk minimisation measures by safety concern*

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures (only routine risk minimisation measures)

VI.2.6 *Planned post authorisation development plan*

Study title Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances.				
Not applicable				
Category 3 - Required additional pharmacovigilance activities **(Food and Drug Administration requirement)**				
	To obtain long-term clinical safety information in patients with NAGS	Assess treatment with CGA for:	Study start	Apr 2012

Study 1604-2: A registry of patients, including infants with NAGS deficiency and treated with CGA to obtain long-term clinical safety information. Ongoing	deficiency treated with CGA.	- Use in pregnant women - Patients with cardiac diseases/renal and hepatic impairment -Long-term safety	Study completion	January 2027
Study 1604-3: A study of the effects of CGA on pregnancy and foetal outcomes. Ongoing	To study of the effects of CGA on pregnancy and foetal outcomes.	Assess treatment with CGA for Use in pregnant women.	Study start	Apr 2012
			Study completion	January 2027
RRDUS-PASS-0573: Short and long-term effects of the Carbaglu® treatment of hyperammonaemia due to MMA and PA in the adult and paediatric patient population. Ongoing	Obtain short- and long-term clinical safety data in pediatric and adult patients with PA and MMA treated with Carbaglu.	Assess treatment with CGA for: -Long term safety -Use in pregnant women	Study start	June 2022
			Study completion	December 2032
Category Other studies in the pharmacovigilance plan				
PROTECT Study: Understanding the long-term management of organic acidaemia patients with Carbaglu: A mixed methods approach. Ongoing	To describe the number and duration of decompensation events in patients with a diagnosis of MMA or PA who have been receiving Carbaglu for a minimum of 6 months compared to the number and duration of decompensation events that occurred prior to starting treatment with Carbaglu.	Assess treatment with CGA for long-term safety.	Study start	January 2019
			Study completion	September 2026

VI.2.7 Summary of changes to the Risk Management Plan over time

Table 1. Major changes to the Risk Management Plan over time

Version	Approval date	Change
1.0	25 October 2011	Not applicable; this was the first RMP for carglumic acid.

2.1	06 August 2015	Safety concerns • Important potential risk of 'Lack of efficacy due to a not confirmed diagnosis of the metabolic disease or inadequate low dosing' reworded to 'Lack of efficacy'. • The missing information of 'Effects on pregnancy and foetal outcome' was reworded to 'Use in pregnant women'. • The following missing information was removed: o Bradycardia o Pyrexia related effects o Unknown food and drug interactions • Patients with cardiac diseases/renal and hepatic impairment added as missing information.
3.0	03 June 2019	Conversion of RMP to Good Pharmacovigilance Practices Module V Revision 2. Updates to clinical trial and post-authorisation exposure. Pharmacovigilance Plan: • Updates regarding Study 1604-2 and Study 1604-3. Post-authorisation efficacy plan: • Addition of a Phase I, multicentre, open label, parallel group adaptive pharmacokinetic single dose study of oral carglumic acid in subjects with normal and varying degrees of impaired renal function).
4.0	10 April 2020	Safety concerns: • The important potential risk of lack of efficacy was removed • Long term safety was added as missing information Pharmacovigilance Plan: • Addition of a registry study which evaluates the effect of Carglumic acid in long term for MMA and PA patients
5.0	21 December 2020	Module SII – Non-clinical Part of the Safety Specification • Table 3: Key non-clinical safety findings and relevance to human use • Described the adverse effects on the heart and kidneys in the 2-year carcinogenicity study in rats
6.0	21 June 2022	Safety concerns: No change Part V was updated to note that a lower dose of Carbaglu should be used in patients with renal impairment. Updates to clinical trial and post-authorisation exposure. Pharmacovigilance Plan: Update of the information regarding the studies. Inclusion of the RRDUS-PASS-0573 study.

		Risk minimization measures: Update of the routine risk minimization measures with additional Package Leaflet and SmPC information.