Summary of the Risk Management Plan for Carbaglu (Carglumic acid)

This is a summary of the RMP for Carbaglu. The RMP details important risks of Carbaglu, how these risks can be minimised, and how more information will be obtained about Carbaglu's risks and uncertainties (missing information).

Carbaglu's product information gives essential information to healthcare professionals and patients on how Carbaglu should be used.

This summary of the RMP for Carbaglu should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report. Important new concerns or changes to the current ones will be included in updates of Carbaglu's RMP.

I. The Medicine and What it is Used For

Carbaglu is authorised for hyperammonaemia due to N-acetylglutamate synthase primary deficiency, isovaleric acidaemia, methylmalonic acidaemia and propionic acidaemia (see product information for the full indication). It contains carglumic acid as the active substance and it is given by oral administration.

Further information about the evaluation of Carbaglu's benefits can be found in Carbaglu's European Public Assessment Report, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage:
https://www.ema.europa.eu/en/medicines/human/EPAR/carbaglu.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Carbaglu, together with measures to minimise such risks and the proposed studies for learning more about Carbaglu's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions and advice on correct use, in the product information addressed to patients and healthcare professionals.
- Important advice on the medicine's packaging.
- The authorised pack size – the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.
- The medicine's legal status – the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Carbaglu is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Carbaglu are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Carbaglu. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	None
Important potential risk	None
Important missing information	Use in pregnant women Patients with cardiac diseases/renal and hepatic impairment

II.B Summary of important risks

Summaries of the important risks and missing information for Carbaglu are provided in the following tables.

Missing information of use in pregnant women	
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC Section 4.6. Package Leaftlet (PL) section 2. Section 4.6 of the SmPC for Carbaglu notes that animal studies have revealed minimal developmental toxicity, and that caution should be exercised when prescribing to pregnant women. 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.
Additional pharmacovigilance activities	Study 1604-2 and Study 1604-3 (US FDA post approval requirements)

SmPC=Summary of Product Characteristics.

Missing information of patients with cardiac diseases/renal and hepatic impairment	
Risk minimisation measures	SmPC Sections 4.2 and 4.4 PL section 2 and 3. <u>Routine risk minimisation measures:</u> 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 of the SmPC for Carbaglu notes that limited data on the safety of Carbaglu are available. Therefore, Section 4.4 of the SmPC notes that systematic surveillance of liver, renal and cardiac functions, as well as 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.
Additional pharmacovigilance activities	Study 1604-2 (US FDA post approval requirement).

SmPC=Summary of Product Characteristics.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

The following studies are being conducted as post-marketing requirements from the Food and Drug Administration:

<u>Study 1604-2</u>

Purpose of the study: To obtain long-term clinical safety information in patients with N-acetylglutamate synthase deficiency treated with Carbaglu.

<u>Study 1604-3</u>

Purpose of the study: To study of the effects of Carbaglu on pregnancy and fetal outcomes.

II.C.2 Other studies in post-authorisation development plan

Not applicable.