Part VI: Summary of the risk management plan by product

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	Medication error (including incorrect route of administration) Off label use
Missing information	Use in pregnant women Patients with cardiac diseases/renal and hepatic impairment

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

Not applicable

VI.1.3 Summary of Post authorisation efficacy development plan

Not applicable

VI.1.4 Summary table of Risk Minimisation Measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important Identified Risks		
None	**Not applicable**	**Not applicable**
Important Potential Risks		
Medication error (including incorrect route of administration)	Proposed text in "Posology and Method of Administration" in Section 4.2 of SmPC states: 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. • Prescription only medicine • Use restricted to physicians experienced in the treatment of metabolic disorders	None
Off label use	• Proposed text in "Therapeutic indication" in Section 4.1 of SmPC states: Carglumic Acid 200 mg Dispersible Tablets are indicated in the treatment of • hyperammonaemia due to Nacetylglutamate synthase primary deficiency • Prescription only medicine • Use restricted to physicians experienced in the treatment of metabolic disorders.	

Missing Information		
Use in pregnant women	Proposed text in "Fertility, pregnancy and lactation" in section 4.6 of SmPC states: For carglumic acid no clinical data on exposed pregnancies are available. Animal studies have revealed minimal developmental toxicity. Caution should be exercised when prescribing to pregnant women. 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. Therefore, breast-feeding during the use of carglumic acid is contraindicated. Prescription only medicine Use restricted to physicians experienced in the treatment of metabolic disorders.	None
Patients with cardiac disease/renal and hepatic impairment	Proposed text in "Special warning and precaution for use" in section 4.4 of SmPC states: "As very few data on the safety of carglumic acid are available, systematic surveillance of liver, renal, cardiac functions and haematological parameters is recommended." • Prescription only medicine • Use restricted to physicians experienced in the treatment of metabolic disorders.	

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Carglumic acid is prescribed to decrease high ammonia levels in the blood. A high level of ammonia is especially toxic for the brain and can lead, in severe cases, to reduced levels of consciousness and coma. The increased ammonia level in blood may occur due to the lack of a specific liver enzyme (N-acetylglutamate synthase). The deficiency of this liver enzyme is a very rare inborn metabolic disorder. Patients with this disorder are not able to eliminate nitrogen waste, which builds up after eating protein. This disorder persists throughout the life of the affected patient, requiring lifelong treatment. The estimated prevalence of this specific liver enzyme (N-acetylglutamate synthase) deficiency is 0.00125 per 10,000 persons in the European Union.

VI.2.2 Summary of treatment benefits

Numerous scientific studies have shown favourable treatment benefits with carglumic acid in patients with N-acetylglutamate synthase (NAGS) deficiency. Treatment with carglumic acid has shown a quick and consistent therapeutic response. The majority of patients treated with carglumic

acid ate a normal protein intake which aids normal growth and makes it simpler to comply with treatment. The outcome of carglumic acid treatment included a high survival rate and high quality of life due to reduced toxic effects of ammonia on the brain. Regular and adequate dose of carglumic acid ensures the continuous and consistent control of ammonia and glutamine level in blood, which helps patients in preserving the integrity and functionality of vital organs over time. The published data and safety profile of carglumic acid further supports the use of carglumic acid in patients with NAGS deficiency.

The data presented for the authorisation of the reference medicinal product Carbaglu to support the efficacy of Carglumic acid in NAGS deficiency consisted of a retrospective series of 20 patients (plus an update on 2 cases that started treatment in 2001) evaluable for safety – (not all had NAGS deficiency) of which 12 were evaluable for efficacy that received chronic treatment with Carglumic Acid (the 2 new cases were also confirmed or suspected NAGS deficient patients). The other 8 patients were treated for hyperammonaemia of another cause (5 cases with other urea cycle disorders due to defects in other enzymes associated with the urea cycle, including 3 carbamoylphosphate synthetase and 2 ornithine transcarbamoylase defects, and 3 cases of fatty acid oxidation disorder).

Results showed that overall, plasma ammonia levels were well controlled. Furthermore, the following results were also reported,

- In 5 patients, ammonaemia was always found normal.
- In 3 patients, an abnormal value was measured on a single occasion: infection with high fever, very low Carglumic Acid dose (10 mg/kg/d), unknown cause in the last case.
- In 3 patients, there were transient fluctuations slightly above the upper normal value: only at the start of Carglumic Acid after a very fast reduction of the dose in the first patient; in 2 of the 3 siblings despite concomitant treatment.
- In one patient, fluctuating ammonia levels decreased from 120 - 160 μmol/l before NCGA to 90 μmol/l but never normalised.

VI.2.3 Unknowns relating to treatment benefits

It is recommended to test individual responsiveness to carglumic acid before initiating any long term treatment. For example:

- In a child in state of coma, treatment should be started with a dose of 100 to 250 mg/kg/day and level of ammonia concentration in plasma should be measured at least before each administration; it should normalise within a few hours after starting carglumic acid.
- In a patient with moderate increase in ammonia in blood (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.
- Very limited safety data is available regarding the use of Carglumic acid with cardiac disease, renal or hepatic impairment. As a result, patients should be closely monitored in

terms of their liver, renal and cardiac functions. Furthermore, haematological (blood) parameters should be monitored.

- No clinical data on exposed pregnancies are available for carglumic acid. Caution should be exercised when prescribing to pregnant women.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
None	Not applicable	Not applicable

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Medication error (including incorrect route of administration)	Carglumic acid tablets are designed to be dispersed in tap water and swallowed. The tablet dispersion is not sterile and is not suitable for administration by injection (for instance into the vein). The tablet dispersion may be administered from a syringe via a nasogastric tube so care must be taken to ensure that the syringe containing the carglumic acid is not injected if the patient is receiving injected medications at the same time.
Off label use (Use of medication for indications not mentioned in Patient Information leaflet)	Carglumic Acid 200 mg dispersible tablets are only indicated for the treatment of n-acetylglutamate synthetase (NAGS) deficiency. The product is not to be used for the treatment of isovaleric acidaemia (disease where body unable to process proteins), propionic acidaemia and methylmalonic acidaemia (diseases where body is unable to process protein and fats).

Missing information

Risk	What is known
Use in pregnant women	• Animal studies have revealed minimal developmental toxicity (adverse effects on developing babies). As little information is available the drug should only be used in pregnant women when the benefits are thought to outweigh the risks to the baby. • 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. Therefore, women should not breast-feed during the use of carglumic acid.
Patients with cardiac (heart) diseases/renal (kidney) and hepatic (liver) impairment (loss of full functioning))	Very limited safety data is available for use of Carglumic acid with cardiac disease, and renal or hepatic impairment. As a result such patients should be closely monitored in terms of their liver, renal and
Risk	**What is known**
	cardiac functions when treated with the drug. Furthermore, haematological (blood) parameters should be monitored.

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.

The Summary of Product Characteristics and the Package leaflet for carglumic acid can be found in the carglumic acid's EPAR page.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

None

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

Not applicable – first Risk Management Plan for carglumic acid