Part VI: Summary of the Risk Management Plan

Summary of risk management plan for RAVICTI (glycerol phenylbutyrate)

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

RAVICTI's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how RAVICTI should be used.

This summary of the RMP for RAVICTI 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 (EPAR).

Important new concerns or changes to the current ones will be included in updates of RAVICTI's RMP.

I. The medicine and what it is used for

RAVICTI is authorized for use as adjunctive therapy for chronic management of patients with urea cycle disorders (UCDs) (see SmPC for the full indication). It contains glycerol phenylbutyrate as the active substance and it is given by oral administration.

Further information about the evaluation of RAVICTI's benefits can be found in RAVICTI's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/ravicti.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

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

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

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized 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 minimize its risks.

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

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including PSUR 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 RAVICTI is not yet available, it is listed under 'missing information' below.

II. A List of important risks and missing information

Important risks of RAVICTI are risks that need special risk management activities to further investigate or minimize 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 RAVICTI. 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 risks	• Toxicity due to the active metabolite PAA (Phenylacetic acid) • Carcinogenicity
Missing information	• Use in patients with renal impairment • Exposure during pregnancy and lactation • Long-term safety

II. B Summary of important risks

Important potential risk: Toxicity due to the active metabolite PAA (Phenylacetic acid)	
Evidence for linking the risk to the medicine	Evidence source: clinical trials, scientific literature Strength of evidence: The major metabolite of RAVICTI, PAA, is associated with neurotoxicity. Signs and symptoms of PAA neurotoxicity, including somnolence, fatigue, light-headedness, headache, dysgeusia, hypoacusis, disorientation, impaired memory, and exacerbation of pre-existing neuropathy, were observed at plasma PAA concentrations of 500 µg/mL in a study of adult cancer

Important potential risk: Toxicity due to the active metabolite PAA (Phenylacetic acid)	
	patients who were administered PAA intravenously [Thibault et al., 1995]. In healthy subjects, after administration of 4 mL and 6 mL RAVICTI 3 times daily (13.2 g/day and 19.8 g/day, respectively) for 3 days, a dose-dependent increase in non-serious nervous system adverse reactions were observed. In subjects who had nervous system adverse reactions, plasma PAA concentrations, which were measured on Day 3 per protocol and not always at onset of symptoms, ranged from 8 to 56 micrograms/mL with 4 mL RAVICTI 3 times daily and from 31 to 242 micrograms/mL with 6 mL RAVICTI 3 times daily. Although reversible clinical manifestations of PAA neurotoxicity have not been seen in clinical trials involving UCD patients, high PAA levels should be suspected in patients (particularly in children < 2months) with unexplained somnolence, confusion, nausea and lethargy who have normal or low ammonia.
Risk factors and risk groups	Patient groups at risk for elevated PAA levels would include pediatric patients (age 2 years or younger) dosed at the maximum level and patients with hepatic decompensation.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.2 where advice to measure plasma PAA and plasma PAA to phenylacetylglutamine (PAGN) ratio and details on dose adjustments are provided • SmPC Section 4.4, and 4.9 Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: HZNP-RAV-401 EU PASS in partnership with European Registry and Network for Intoxication Type Metabolic Diseases(E-IMD) See section II. C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Carcinogenicity	
Evidence for linking the risk to the medicine	Evidence source: non-clinical data Strength of evidence: Animal studies in rats have shown increases in the incidence of various treatment-related tumors. An SAP unanimously concluded that none of the findings in rats suggested a substantive cancer risk to UCD patients treated with RAVICTI. Most findings were considered rodent specific with no relevant counterpart in humans. The period of observation in the clinical

Important potential risk: Carcinogenicity	
	trials to date is too limited to detect ADRs potentially related to carcinogenicity.
Risk factors and risk groups	No risk groups have been identified.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 5.3 Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: HZNP-RAV-401 EU PASS (E-IMD) See section II. C of this summary for an overview of the post-authorisation development plan.

Missing information: Use in patients with renal impairment	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.2 including recommendation to maintain lowest necessary dose • SmPC Section 5.2 • PL Section 2 and 3 Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: HZNP-RAV-401 EU PASS (E-IMD) See section II. C of this summary for an overview of the post-authorisation development plan.

Missing information: Exposure during pregnancy and lactation	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4, and PL Section 2 where advice to use effective contraceptive measures by women of child-bearing potential • SmPC Section 4.6and 5.3 Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: HZNP-RAV-401 EU PASS (E-IMD) See section II. C of this summary for an overview of the post-authorisation development plan.

Missing information: Long-term safety	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.8 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: HZNP-RAV-401 EU PASS (E-IMD) See section II. C of this summary for an overview of the post-authorisation development plan.

II. C Post-authorisation development plan

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

The following studies are conditions of the marketing authorisation:

Study short name: HZNP-RAV-401 EU PASS (E-IMD)

Purpose of the study: Due to the low incidence and low prevalence of the UCDs, RAVICTI is classified as an orphan medicinal product for the treatment of UCD in the EU/EEA. Due to the rarity of UCD it was unfeasible to conduct studies in significantly larger populations and only a limited number of patients have been exposed to RAVICTI for a long-term period. Furthermore, the clinical development program did not include pregnant or lactating females and patients with renal impairment. Therefore, the safety profile of RAVICTI in these patient populations and long-term safety has been recognized as missing information during the European Authorization procedure and Immedica Pharma AB has committed to conduct a post-authorization registry to collect additional data. The registry will also focus on additional information on the incidence rate and type of cancer in the patient population and PAA toxicity.

Overall, the registry is established to further evaluate and characterize the safety profile of RAVICTI and track long-term outcomes in UCD patients treated with RAVICTI and will thereby further allow conclusions about the safety and efficacy of patients not studied in the clinical development program including pediatric patients.

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

There are no other studies required for RAVICTI.