Summary of the EU Risk Management Plan (RMP) of QARZIBA®

Medicinal product: QARZIBA

Active substance(s): Dinutuximab beta

Marketing Authorisation Holder: Medius AG

RMP Version number: EU RMP Version number 10.0

RMP Date of final sign off: 5-May-2021

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 Qarziba 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 Qarziba in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Medius AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Qarziba.

I. The medicine and what it is used for

Qarziba is indicated for the treatment of high-risk neuroblastoma in patients aged 12 months and above, who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and SCT, as well as patients with history of relapsed or refractory neuroblastoma, with or without residual disease. Prior to the treatment of relapsed neuroblastoma, any actively progressing disease should be stabilised by other suitable measures.

In patients with a history of relapsed/refractory disease and in patients who have not achieved a complete response after first line therapy, Qarziba should be combined with IL-2 (see SmPC for the full indication). It contains dinutuximab beta as the active substance and it is given by infusion.

Further information about the evaluation of Qarziba's benefits can be found in Qarziba's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003918/human_med_0 02104.jsp&mid=WC0b01ac058001d124.

II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of Qarziba, together with measures to minimise such risks and the proposed studies for learning more about Qarziba'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 package leaflet and SmPC 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 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 Qarziba is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Qarziba are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. 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 Qarziba.

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);

Summary of Safety Concerns	
Important identified risks	• Pain • Serious infusion reactions including hypersensitivity, hypotension, and CRS • Neurological eye disorders • Peripheral neuropathy • Capillary leak syndrome • Hypoxia, respiratory distress and respiratory failure • Haematological toxicities
Important potential risks	• Cardiotoxicity • Immunogenicity • Medication errors
Missing information	• Long-term effects of treatment in childhood • Use in adolescents

II.B Summary of important risks

Important identified risk 1: Pain	
Evidence for linking the risk to the medicine	**Clinical trials**: Most patients treated with dinutuximab beta experienced pain despite pre-treatment with analgesics. Pain typically occurred during the first infusion of dinutuximab beta and decreased over the treatment courses.
Risk factors and risk groups	Neuropathic pain depends on infusion rates, i.e. decreased infusion rates are associated with less neuropathic pain. Otherwise no risk factors are known for neuropathic pain.
Risk minimisation measures	**Routine risk minimisation measures**: SmPC sections: 4.4, 4.8 **Additional risk minimisation measures**: None
Additional pharmacovigilance activities	EUSA DB 0001, APN311-202, APN311-304

Important identified risk 2: Serious infusion reactions including hypersensitivity, hypotension, and CRS	
Evidence for linking the risk to the medicine	**Non-clinical:** Abscess, fibrosis, granulation tissue, haemorrhage, granulomatous inflammation or chronic active inflammation were seen in animal treated with dinutuximab beta. **Clinical trials**: Infusion-related reactions including hypersensitivity reactions were reported in patients treated with dinutuximab beta like allergic reaction, hypotension, and CRS. **Class effect:** Humanised monoclonal antibodies share a risk for infusion reactions, most of which occur with the first dose. • **Rituximab** (CD20-specific): very common or common (77% of patients) • **Cetuximab** (EGFR-specific): mild and moderate: very common; severe: common (serious in up to 3% of patients, fatal in 0.1% (51)) • **Infliximab** (TNFα-specific): very common (up to 18% of patients; serious in 0.4%) • **Basiliximab** (IL-2 receptor α-chain specific): frequencies not available. • **Abciximab** (c7E3 Fab-specific): anaphylactic reaction/ hyper- sensitivity/allergic reactions: rare
Risk factors and risk groups	The severity of infusion reactions directly correlates with the amount of lymphocytes (the greater the amount of circulating lymphocytes, the higher the risk and severity of immune-related reactions (Chung 2008)). The risk of anaphylactic reactions is increased in patients with a history of allergy to red meat or to bites or positive results or tests of IgE antibodies against dinutuximab beta. Further risk factors include: diagnosis of asthma, atopic patients, concomitant β-adrenergic blocker therapy, concurrent autoimmune disease, female sex, higher than standard drug doses, iodine or seafood allergies, haematologic malignancies, history of drug allergy, pre-existing cardiac or pulmonary dysfunction (Vogel 2010). Concomitant IL-2 increases risk if infusion reactions.
Risk minimisation measures	**Routine risk communication**: SmPC sections: 4.2, 4.4, 4.8 **Additional risk minimisation measures**: None
Additional pharmacovigilance activities	EUSA DB 0001

Important identified risk 3: Neurological eye disorders	
Evidence for linking the risk to the medicine	**Clinical trials**: Neurological eye disorders were observed across studies in patients treated with dinutuximab beta like impaired visual accommodation, mydriasis, blurred vision or photophobia.
Risk factors and risk groups	Not known
Risk minimisation measures	**Routine risk minimisation measures**: SmPC sections: 4.2, 4.4, 4.8 **Additional risk minimisation measures**: None
Additional pharmacovigilance activities	EUSA DB 0001

Important identified risk 4: Peripheral neuropathy	
Evidence for linking the risk to the medicine	**Clinical trials**: Both motor and sensory peripheral neuropathies have been reported in patients treated with dinutuximab beta.
Risk factors and risk groups	Concomitant IL-2 treatment.
Risk minimisation measures	**Routine risk minimisation measures**: SmPC sections: 4.2, 4.4, 4.8 **Additional risk minimisation measures**: None
Additional pharmacovigilance activities	EUSA DB 0001

Important identified risk 5: Capillary leak syndrome	
Evidence for linking the risk to the medicine	**Clinical trials**: Capillary leak syndrome was reported across studies in patients treated with dinutuximab beta.
Risk factors and risk groups	Co-administration of IL-2.
Risk minimisation measures	**Routine risk minimisation measures**: SmPC sections: 4.2, 4.4, 4.8 **Additional risk minimisation measures**: None
Additional pharmacovigilance activities	EUSA DB 0001

Important identified risk 6: Hypoxia, respiratory distress and respiratory failure	
Evidence for linking the risk to the medicine	**Clinical trials**: Events related to hypoxia, respiratory distress and respiratory failure were observed across studies in patients treated with dinutuximab beta.
Risk factors and risk groups	IL-2 co-administration, infections, sepsis, pulmonary disease, overdose of certain drugs (opiates, thiazides), gemcitabine, pancreatitis, chemotherapy, XRT to the lungs, premature delivery.
Risk minimisation measures	**Routine risk minimisation measures**: SmPC sections: 4.4, 4.8 **Additional risk minimisation measures**: EUSA DB 0001

Important identified risk 7: Haematological toxicities	
Evidence for linking the risk to the medicine	**Non-clinical trials:** In Guinea pigs, statistically significant decreases in numbers of white blood cells, reticulocytes, and platelets compared with control animals were observed. **Clinical trials:** Occurrence of haematologic toxicities has been reported with Qarziba. **Class effect:** • **Abciximab** (platelet-glycoprotein IIb/IIIa-specific): acute thrombocytopenia develops after first infusion of abciximab in about 1% of patients. Acute thrombocytopenia occurs in more than 10% of patients after a second infusion (Hansel et al. 2010). • **Bevacizumab** (VEGF-specific): febrile neutropenia, leucopoenia, neutropenia, thrombocytopenia: very common; anaemia, lymphopenia: common. • **Infliximab** (TNFα-specific): anaemia, neutropenia, leucopoenia: common thrombocytopenia, lymphopenia, lymphocytosis: uncommon. • **Rituximab** (CD20-specific): neutropenia, leucopoenia, febrile neutropenia, thrombocytopenia: very common; anaemia, granulocytopenia: common.
Risk factors and risk groups	Concomitant treatment with IL-2, inadequate haematologic function, chemotherapy, SCT, bone marrow involvement in neuroblastoma.
Risk minimisation measures	**Routine risk minimisation measures**: SmPC sections: 4.4, 4.8 **Additional risk minimisation measures**: None
Additional pharmacovigilance activities	APN311-302

Important potential risk 1: Cardiotoxicity	
Evidence for linking the risk to the medicine	**Clinical trials**: Cardiac events were reported across studies in patients treated with dinutuximab beta.
Risk factors and risk groups	IL-1 co-administration
Risk minimisation measures	**Routine risk minimisation measures**: SmPC sections: 4.8 **Additional risk minimisation measures**: None
Additional pharmacovigilance activities	EUSA DB 0001

Important potential risk 2: Immunogenicity	
Evidence for linking the risk to the medicine	**Non-clinical trials**: ADAs were detected in most animals on Day 34 and on Day 61. **Clinical trials**: Measurable ADA titres were detected in patients treated with dinutoximab beta. Additional review of data indicated that ADA do not have any impact on the safety or efficacy of dinutuximab beta. **Class effect**: The development of ADAs is a class effect of monoclonal chimeric antibodies.
Risk factors and risk groups	An activated immune system (e.g. patients with certain infections or autoimmune disease), patient age (i.e. increased risk in newborns (Cuenca et al. 2013), history of allergy, prior exposure to a similar protein product, sensitisation to the excipients of the product, dose and frequency of administration (e.g. a lower dose administered intermittently may be more immunogenic than a larger dose administered without interruption), genetic factors (i.e. some HLA haplotypes may predispose patients to undesirable antibody responses) (Rosenberg and Worobec 2004).
Risk minimisation measures	**Routine risk minimisation measures**: SmPC sections: 5.1 **Additional risk minimisation measures**: None
Additional pharmacovigilance activities	APN311-202 and APN311-304

Important potential risk 3: Medication errors	
Evidence for linking the risk to the medicine	No errors involving dinutuximab beta occurred during the clinical development programme.

Risk factors and risk groups	Not applicable
Risk minimisation measures	**Routine risk minimisation measures**: SmPC sections: 4.2 **Additional risk minimisation measures**: None

Missing information 1: Long-term effects of treatment in childhood	
Risk minimisation measures	**Routine risk minimisation measures**: None **Additional risk minimisation measures**: None
Additional pharmacovigilance activities	EUSA DB 0001

Missing information 2: Use in adolescents	
Risk minimisation measures	**Routine risk minimisation measures**: None **Additional risk minimisation measures**: None
Additional pharmacovigilance activities	In order to better define the posology in children over the entire age range and the impact of HACAs on PD, efficacy and safety, the MAH will submit the results of an evaluation of plasma samples collected from patients in studies APN311-202v1-2-3 and APN311-304.

II.C Post-authorisation development plan

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

Study name	**Rationale and study objectives**
EUSA DB 0001	Neuroblastoma, is the most common extra-cranial solid tumour in children. Most patients with neuroblastoma are diagnosed under the age of 5 years and most present with metastatic disease and/or high-risk features. Despite the introduction of novel treatment strategies, including high-dose chemotherapy followed by ASCT, the outcome of these patients remains poor.

	Dinutuximab beta is a chimeric monoclonal IgG1 antibody that is specifically directed against the carbohydrate moiety of GD2, which is overexpressed on neuroblastoma cells. By binding to neuroblastoma cells, dinutuximab beta can induce both CDC and ADCC. The primary objective of this patient registry is to assess: • Pain severity and use of analgesics during treatment • Incidence of neurotoxicity, visual impairment, capillary leak syndrome, cardiovascular events and hypersensitivity reactions. • Long term safety Secondary objectives are to assess: • PFS • EFS • OS
Evaluation of PK and immunogenicity profile from completed and ongoing studies (studies APN311-202 v1-v2-v3 and APN311-304)	To collect PK and immunogenicity data from completed and ongoing studies (studies APN311-202 v1-v2-v3 and APN311-304) using fully analytical validated drug and HACA assays that cover the time course of exposure. This study will provide further data in order to better define the posology in children over the entire age range and the impact of HACAs on PD, efficacy and safety. It will address the exposure-efficacy relationship. It will also evaluate the benefit of completing all treatment cycles after developing HACAs.
Study APN311-202 after amendment 3. Multicentre, open-label randomised, controlled study in R/R and high risk patients	To assess add-on effect of IL-2 (efficacy and safety) in the R/R setting, 10 mg/m²/day APN311 administered as continuous infusion over 10 days ± s.c. IL-2 + 13-cis-RA (five 35-day cycles).
Survival results of studies APN311-202 and 302 (at least 5 years)	Current survival data are immature and long-term survival cannot be estimated. Objective is to provide further survival data

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

None