Gazyvaro® (Obinutuzumab)

Public Risk Management Plan (RMP) Summary

Konzentrat zur Herstellung einer Infusionslösung, 1000 mg/ 40 ml, Zul.-Nr 63172

Document Version 2.0
Document Date: 25.11.2021
Based on EU-RMP Version 8.0

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

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PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR GAZYVARO (OBINUTUZUMAB)

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

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

This summary of the RMP for Gazyvaro 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 Gazyvaro's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Gazyvaro is authorized for chronic lymphocytic leukemia and non-Hodgkin lymphoma (See SmPC for full indication). It contains obinutuzumab as the active substance and it is given by intravenous route.

Further information about the evaluation of Gazyvaro's benefits can be found in Gazyvaro EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERIZE THE RISKS

Important risks of Gazyvaro, together with measures to minimize such risks and the proposed studies for learning more about Gazyvaro 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.

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In addition to these measures, information about adverse events is collected continuously and regularly analyzed including periodic safety update report assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of Important Risks and Missing Information

Important risks of Gazyvaro are risks that need special risk management activities to further investigate or minimize 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 Gazyvaro. 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	Infusion related reactions Infections Thrombocytopenia Worsening of pre-existing cardiac conditions
Important potential risks	Second malignancies
Missing information	None

II.B Summary of Important Risks

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Important identified risk -	
Evidence for linking the risk to the medicine	Clinical trial data from studies BO20999, BO21000, BO21003, BO21004, BO21005, BO21223, GAO4753g, GAO4768g, GAO4779g, GAO4915g, and MO40597.

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Risk factors and risk groups	The following specific patient characteristics were suggested to be potential risk factors for CLL patients who experienced IRRs related to obinutuzumab in Study BO21004 by the study Data Safety Monitoring Board (DSMB) in September 2011. High tumor burden (circulating lymphocyte count >100 x10^9/L) Binet stage C CLL at screening (Rai III/IV) Low body mass index (BMI <20) Hypertension necessitating anti-hypertensive treatment. A risk factor analysis of the Stage 2 data from Study BO21004 did not allow clear identification of the patients at a higher risk of IRRs. Increased tumor burden is considered a risk factor for IRR. However, no clear effect of tumor burden (as assesses by circulating lymphocyte count ≥100×10^9 cells/L) was seen on the incidence of IRRs. In the GClb arm of BO21004 (Stage 2 analysis), there was no difference in IRR incidence based on tumor burden. The incidence of all grade IRRs in patients with high tumor burden was 67% and in patients with a low tumor burden, it was 66%. Similarly, the incidence of grade 3-4 IRRs was also comparable in patients with high and low tumor burden (22% vs. 19%). The incidence of IRRs as per Binet staging at baseline was analyzed. The incidence of all grade IRRs was comparable in patients with Binet stage A and C and lower in patients with Binet stage B at baseline (A, B, C: 67%, 57%, 75%). A similar trend was seen with grade 3-4 (23%, 13%, 26%) and serious IRRs (11%, 8%, 12%). The incidence of all grade and Grade 3-4 IRRs in the GClb arm was comparable in patients with body mass index (BMI) < 20 and ≥ 20 (all grades 60% vs. 66% and Grade 3-4, 20% vs. 20%). The incidence of IRRs remained the same irrespective of whether patients received anti-hypertensive treatment or not (all grade IRR, 66% vs 66%, and Grade 3-4, 20% vs. 19%). In addition to the analysis of risk factors proposed by the DSMB, an extensive risk factor analysis was also performed in patients who developed an IRR compared to patients who did not experience any IRR event based on the characteristics of patients at baseline. These included age, gender, BMI (median BMI and BMI>30), estimated creatinine clearance (median CrCl and CrCl< or ≥70ml/min), radiologically assessed sum of product of diameters for target lesions, circulating lymphocyte count (median lymphocyte count, count >25x10^9 cells/L and count>100x10^9 cells/L) and medical history of diabetes, coronary artery disease, hypertension and hypercholesterolemia. Assessment of all the above-mentioned potential risk factors revealed no conclusive differences in baseline characteristics of patients with or without IRRs.

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Important identified risk -	
	In Study MO40597, the incidence of nature of IRRs after short-duration infusion at Cycle 2 and subsequent cycles in patients with FL was similar to that observed in patients receiving standard-duration infusion.
Risk minimization measures	**Routine risk communication:** Section 4.2 of the EU SmPC: Posology and method of administration Section 4.4 of the EU SmPC: Special warnings and precautions for use Section 4.8 of the EU SmPC: Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Corticosteroid premedication is recommended for patients with FL and mandatory for CLL patients in the first cycle. Premedication to reduce the risk of infusion related reactions. Hypotension, as a symptom of IRRs, may occur during Gazyvaro intravenous infusions. Therefore, withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each Gazyvaro infusion and for the first hour after administration. Patients who have pre-existing cardiac or pulmonary conditions should be monitored carefully throughout the infusion and the post-infusion period. Refer to section 4.4 of the SmPC for detailed information. **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Gazyvaro is a prescription only medicine **Additional risk minimization measures** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

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Important identified risk-	
Evidence for linking the risk to the medicine	Clinical trial data from studies BO20999, BO21000, BO21003, BO21004, BO21005, BO21223, GAO4753g, GAO4768g, GAO4779g, GAO4915g, and MO40597.
Risk factors and risk groups	Patients with CLL and NHL are predisposed to common as well as opportunistic infections as a result of a number of disease-related factors including B cell dysfunction, immunoglobulin deficiency, abnormal T-cell function, and neutropenia resulting from infiltration of the bone marrow.
Risk minimization measures	**Routine risk communication:** Section 4.4 of the EU SmPC: Special warnings and precautions for use Section 4.8 of the EU SmPC: Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Gazyvaro should not be administered in the presence of an active infection and caution should be exercised when considering the use of Gazyvaro in patients with a history of recurring or chronic infections. Refer to section 4.4 and 4.8 of the SmPC for detailed information. **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Gazyvaro is a prescription only medicine **Additional risk minimization measures:** None
Additional pharmacovigilance activities	None

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Important identified risk-Thrombocytopenia	
Evidence for linking the risk to the medicine	Clinical trial data from studies BO20999, BO21000, BO21003, BO21004, BO21005, BO21223, GAO4753g, GAO4768g, GAO4779g, GAO4915g, and MO40597.
Risk factors and risk groups	No specific risk factors have been identified by Roche for non-acute thrombocytopenia (i.e. thrombocytopenia occurring more than 24 hours after obinutuzumab infusion). However, possible risk factors for acute thrombocytopenia (based on the published rituximab literature), may be high tumor burden, bone marrow involvement, splenomegaly and histological subtypes of mantle cell lymphoma and hairy cell leukemia. In general, patients with CLL appear to be more at risk of thrombocytopenia than NHL patients.
Risk minimization measures	**Routine risk communication:** Section 4.4 of the EU SmPC: Special warnings and precautions for use Section 4.8 of the EU SmPC: Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Patients should be closely monitored for thrombocytopenia, especially during the first cycle; regular laboratory tests should be performed until the event resolves, and dose delays should be considered in case of severe or life-threatening thrombocytopenia. Refer to section 4.4 and 4.8 of the SmPC for detailed information. **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Gazyvaro is a prescription only medicine **Additional risk minimization measures:** None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study BO21223 (See Section II.C of this summary for an overview of the post-authorization development plan)

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Important identified risk-Worsening of pre-existing cardiac conditions	
Evidence for linking the risk to the medicine	Clinical trial data from studies BO20999, BO21000, BO21003, BO21004, BO21005, BO21223, GAO4753g, GAO4768g, GAO4779g, GAO4915g, and MO40597.
Risk factors and risk groups	The incidence of CLL and NHL rises markedly with age. Similarly, cardiac events such as heart failure are primarily diseases of aging, with 75% of existing and new cases occurring in individuals over 65 years of age. Concomitant chemotherapy (for example bendamustine and cyclophosphamide) and radiation are also associated with cardiac effects.
Risk minimization measures	**Routine risk communication:** Section 4.4 of the SmPC- Special warnings and precautions for use Section 4.8 of the SmPC- Undesirable Effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Patients with a history of cardiac disease should be monitored closely. In addition, these patients should be hydrated with caution in order to prevent a potential fluid overload. Refer to Section 4.4 and 4.8 of the SmPC for detailed information **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Gazyvaro is a prescription only medicine **Additional risk minimization measures:** None
Additional pharmacovigilance activities	None

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Important potential risk-Second malignancies	
Evidence for linking the risk to the medicine	Clinical trial data from studies BO20999, BO21000, BO21003, BO21004, BO21005, BO21223, GAO4753g, GAO4768g, GAO4779g, GAO4915g, and MO40597.
Risk factors and risk groups	CLL and FL may transform into an aggressive large-cell lymphoma (called Richter's transformation in CLL) or prolymphocytic leukemia. In addition, patients treated for CLL and NHL can develop therapy-related myelodysplastic syndrome or acute myeloid leukemia. Patients with CLL and NHL may also have a higher risk of developing secondary solid tumors. Exposure to genotoxic agents such as alkylating agents, topoisomerase inhibitors and radiation are particularly relevant for patients with NHL or CLL.
Risk minimization measures	**Routine risk communication:** Section 4.8 of the EU SmPC: Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Gazyvaro is a prescription only medicine **Additional risk minimization measures:** None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study BO21223 (See Section II.C of this summary for an overview of the post-authorization development plan)

II.C Post-authorization development plan

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

There are no studies which are conditions of the marketing authorization or specific obligation of Gazyvaro.

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

Study short name: Study BO21223- A multicenter, phase III, open-label, randomized study in previously untreated patients with advanced indolent non-hodgkin's lymphoma evaluating the benefit of GA101 (RO5072759) plus chemotherapy compared with rituximab plus chemotherapy followed by GA101 or rituximab maintenance therapy in responders.

Purpose of the study: The main objective is to evaluate the efficacy of obinutuzumab plus chemotherapy followed by obinutuzumab maintenance therapy compared with rituximab plus chemotherapy followed by rituximab maintenance therapy in previously untreated advanced

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follicular lymphoma. Additionally, it aims to evaluate and compare the safety profiles between the two arms.

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