MABTHERA®
Konzentrat zur Herstellung einer Infusionslösung, 100 mg/10 ml, 500 mg/50 ml
Zul.-Nr. 54’378

Public Risk Management Plan (RMP) Summary

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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 “MabThera” 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 “MabThera” 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 “MabThera”.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR MABTHERA®

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

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

This summary of the RMP for MabThera® should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of 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 MabThera® RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

MabThera® is authorized for Rheumatoid Arthritis, Granulomatosis with Polyangiitis and Microscopic Polyangiitis, Pemphigus Vulgaris, Non-Hodgkin's Lymphoma (SC and IV), Chronic Lymphocytic Leukemia (SC and IV) (see SmPC for the full indication). It contains Rituximab as the active substance and it is given by subcutaneous and intravenous route.

Further information about the evaluation of MabThera® benefits can be found in MabThera® 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 CHARACTERISE THE RISKS

Important risks of MabThera®, together with measures to minimize such risks and the proposed studies for learning more about MabThera® 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 the case of MabThera®, these measures are supplemented with *additional risk minimization* measures mentioned under relevant risks, below.

In addition to these measures, information about adverse events 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 MabThera® is not yet available, it is listed under 'missing Information' below.

II.A LIST OF IMPORTANT RISKS AND MISSING INFORMATION

Important risks of MabThera® 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 MabThera®. 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	• Infections, including serious infections (All Indications) • Progressive multifocal leukoencephalopathy (All Indications) • Hepatitis B reactivation (All Indications) • Hypogammaglobulinemia (Non-oncology indications)
Important potential risks	• Off-label use of the subcutaneous formulation (NHL/CLL SC formulations) • Administration route error (NHL/CLL SC formulations)
Missing information	• Long term use in GPA/MPA patients (GPA/MPA only)

II.B SUMMARY OF IMPORTANT RISKS

Important Identified Risk: Infections, including serious infections (All Indications)	
Evidence for linking the risk to the medicine	MabThera® SmPC Drug Safety Report No 1066792 on Infections (dated March 2016) Drug Safety Report 1027733 on infections (dated, 29 October 2007), and references therein. Drug Safety Report 1022732 on viral infections (dated August 2006) and references therein. Drug Safety Report: 1027731 (dated 29 October 2007), 1044830 (dated 30 June 2011). Genentech Issue Work up (dated 26 October 2007), and references therein. Genentech Issue Work up (dated 26 October 2007) and references therein. **RA** Long-term safety of rituximab: pooled analysis of the RA global clinical trial program over 11 years (cutoff: September 2012) comprising of DANCER (WA17043/U2644g), IMAGE (WA17047/U3373g), MIRROR (WA17044, U2974g), REFLEX (WA17042/IDEC 102-20), SERENE (WA17045/U2973g), SIERRA (U3374g), SUNRISE (U3384g), WA16291, WA16855 (U2653g), WA17531 (IDEC 102-21). Drug Safety Report 1042044 (dated 4 February 2011) on fatal infusion reactions in RA patients, and references therein. **GPA/MPA** RAVE CSR and RAVE Summary of Clinical Safety. Study (WA27893 (RaVeR) Interim CSR • Study ML22514 (MAINRITSAN) CSR and Summary of Clinical safety • DSR 1081144 (cut-off date, 03 March 2017) Evaluation of the Safety Profile of Mabthera Maintenance Therapy in Granulomatosis with Polyangiitis (Wegener's) (GPA) and Microscopic Polyangiitis (MPA) in the Post-Marketing Setting **Pemphigus Vulgaris** • Study ML22196 CSR and Summary of Clinical Safety • DSR 1080390 (data cut-off date: 15 March 2017) a supplemental Safety Report for Rituximab in Pemphigus and Other Autoimmune Indications **NHL/CLL** Data from pivotal studies (cutoff: July 2012) comprising M39021, M39022, M39045, E4494. E1496, PRIMA

Important Identified Risk: Infections, including serious infections (All Indications)	
	(MO18264), CLL8/ML17102, and BO17072/REACH Clinical Study Reports for Study ML17102/CLL 8 and BO17072/REACH and PRIMA (MO18264) studies. • DSR1093782 review of safety data from the use of MabThera/Rituxan in pediatric patients with NHL, CLL and other oncology diseases (cut-off 31 December 2018) CSR 1088458 study Inter B NHL Ritux2010 (11 March 2019
Risk factors and risk groups	**RA, GPA/MPA, PV** Patients with advanced RA are at a higher risk of infection than the general population largely because of altered immunological function or other factors such as decreased mobility, or therapies used to treat the underlying disease (steroids, immunomodulating agents) (Dixon et al. 2006). A retrospective cohort study found that the rate of infection in RA patients was higher than in patients without RA in each of the 11 infection categories examined; sites associated with the highest relative risk were joints, bone, skin and soft tissues (Dixon et al. 2006). Risk factors for infection in GPA/MPA patients include the concomitant use of high dose corticosteroids and/or other immunomodulatory agents. No risk factors have been identified for PV patients. **NHL/CLL** No risk factors or risk groups have been identified specifically for rituximab and the risk of infection is closely related to concomitant chemotherapy and the patient's underlying condition.
Risk minimization measures	**Routine risk communication:** EU SmPC section 4.4: Special warnings and precautions for use EU SmPC Section 4.8: Undesirable Effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:**

Important Identified Risk: Infections, including serious infections (All Indications)	
	Medicine's legal status: Medicinal product subject to restricted medical prescription **Additional risk minimization measures:** Patient Alert Card (non oncology indications) Educational Material for Healthcare Professionals and Educational Material for Patients (non-oncology indications)
Additional pharmacovigilance activities	None

Important identified risk: Progressive Multifocal Leukoencephalopathy (All Indications)	
Evidence for linking the risk to the medicine	• MabThera SmPC • DSR 1096921 Progressive Multifocal Leukoencephalopathy (PML) Cumulative update report for Rituximab, dated January 2019 (cutoff 17 November 2019). • DSR 1081270 Progressive Multifocal Leukoencephalopathy (PML) – Review of reported cases in rituximab-treated patients and potential risk factors, dated 04 September 2017 (cut-off 28 June 2017) • DSR 1074893 Progressive Multifocal Leukoencephalopathy (PML) Cumulative update report for Rituximab, dated 12 January 2017 (cutoff 17 November 2016)) • DSR 1066994 Progressive Multifocal Leukoencephalopathy PML- Cumulative update report for Rituximab, dated 12 January 2016 (cutoff 17 November 2015; submitted with PBRER 1066862 on 20 January 2016), and references therein. • Previous DSRs on PML (and references therein): 1024621 (dated 10 January 2007), abbreviated – 1030699 (dated 21 August 2008), 1038755 (dated 26 April 2010), and 1044761 (dated 11 July 2011). • Six more cumulative updates: 1042104, 1047784, 1050172, 1053546, 1058316, and 1062808 (cutoff 18 November 2010, 17 November 2011, 17 May 2012, 17 November 2012, 17 November 2013, and 17 November 2014, respectively). • Study WA27893 (RaVeR) Interim CSR • Study ML22514 CSR and Summary of Clinical Safety • DSR 1081144 Evaluation of the Safety Profile of Mabthera Maintenance Therapy in Granulomatosis with Polyangiitis (Wegener's) (GPA) and Microscopic Polyangiitis (MPA) in the Post-Marketing Setting • Study ML22196 CSR and Summary of Clinical Safety • DSR 1080390, a supplemental Safety Report for Rituximab in Pemphigus and Other Autoimmune Indications
Risk factors and risk groups	**RA** PML has been reported in patients with autoimmune diseases (including SLE [Systemic Lupus Erythematosus] and RA) who have received immunosuppressive agents.

Important identified risk: Progressive Multifocal Leukoencephalopathy (All Indications)	
	GPA/MPA Cyclophosphamide is a risk factor for development of PML in GPA/MPA patients. **Pemphigus vulgaris** No information available **NHL/CLL** PML almost exclusively occurs in immunocompromised patients. It may occur in patients with deficits in the humoral and/or cellular immune response such as lymphoproliferative diseases, myeloproliferative diseases, carcinomatous diseases and acquired immunodeficiency due to autoimmune diseases and immunosuppressive therapy. Fludarabine has been associated with an increased risk, possibly related to the induction a profound CD4+ lymphopenia
Risk minimization measures	**Routine risk communication:** EU SmPC section 4.4: Special warnings and precautions for use **Routine risk minimization activities recommending specific clinical measures to address the risk:** Patients must be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML. If PML is suspected, further dosing must be suspended until PML has been excluded. Further evalutions, includes MRI scan preferably with contrast, cerebrospinal fluid (CSF) testing for JC Viral DNA and repeat neurological assessments, should be considered. If a patient develops PML, the dosing of MabThera must be permanently discontinued. **Other risk minimization measures beyond the Product Information:** *Medicine's legal status:* Medicinal product subject to restricted medical prescription. **Additional risk minimization measures:** Patient Alert Card (non oncology indications) Educational Material for Healthcare Professionals and Educational Material for Patients (non-oncology indications)
Additional pharmacovigilance activities	None

Important identified risk: Hepatitis B Reactivation (All Indications)	
Evidence for linking the risk to the medicine	• MabThera SmPC • DSRs: 1027731 on opportunistic and reactivation infections (dated 29 October 2007), 1032501 on hepatitis b reactivation in hematology /oncology and autoimmune/RA (dated 18 November 2009), and references therein. **RA and GPA/MPA** DSRs: 1040002 (addendum DSR) on hepatitis B reactivation in RA patients (dated 20 July 2010), 1044079 on hepatitis B and C in RA patients (dated 21 June 2011), 1053039 (addendum DSR) on hepatitis B reactivation in autoimmune and other indications (dated 15 April 2013), and references therein. RAVE Clinical Study Report and RAVE Summary of Clinical Safety. Study WA27893 (RaVeR) Interim CSR Study ML22514 CSR and Summary of Clinical Safety DSR 1081144 (cut-off date, 03 March 2017) Evaluation of the Safety Profile of Mabthera Maintenance Therapy in Granulomatosis with Polyangiitis (Wegener's) (GPA) and Microscopic Polyangiitis (MPA) in the Post-Marketing Setting. **Pemphigus Vulgaris** • Study ML22196 CSR and Summary of Clinical Safety • DSR 1080390,(data cut-off date: 15 March 2017) a supplemental Safety Report for Rituximab in Pemphigus and Other Autoimmune Indications **NHL/CLL** DSRs: 1016003 on hepatitis B reactivation in NHL patients (dated 28 July 2004), 1053039 on hepatitis B reactivation in oncology indications (dated 15 April 2013), and references therein.

Important identified risk: Hepatitis B Reactivation (All Indications)	
Risk factors and risk groups	Patients who have received immunosuppressive therapy for defined periods of time for hematological, oncological or rheumatological diseases and as long term prophylaxis after bone marrow or solid organ transplantation (Calabrese et al. 2007). **NHL/CLL only** HBV reactivation is a well-documented complication of cytotoxic chemotherapy in patients with cancer. Pre-treatment liver function tests and HBV DNA levels have been shown not to correlate with the risk of subsequent development of HBV reactivation. However, male sex, younger age, HBeAg seropositivity, and diagnosis of lymphoma have been reported as risk factors for reactivation. Severe reactivation also appears more likely when the chemotherapy is significantly immunosuppressive, when the viral load is high, and in the presence of precore mutant variant of HBV.
Risk minimization measures	**Routine risk communication:** EU SmPC section 4.4: Special warnings and precautions for use **Routine risk minimization activities recommending specific clinical measures to address the risk:** Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with MabThera. At minimum this should include HBsAg-status and HBcAb-status. These can be complemented with other appropriate markers as per local guidelines. Patients with active hepatitis B disease should not be treated with MabThera. Patients with positive hepatitis B serology (either HBsAg or HBcAb) should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation. **Other risk minimization measures beyond the Product Information:** *Medicine's legal status:* Medicinal product subject to restricted medical prescription. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important identified risk: Hypogammaglobulinemia (non-oncology indications)	
Evidence for linking the risk to the medicine	• MabThera SmPC • Publications referenced within this section. **RA** • Drug Safety Report (DSR): 1042856 on hypogammaglobulinemia, dated 24 August 2011. • DSR 1040916 Prolonged hypogammaglobulinemia, dated September 2010 • Long-term safety of rituximab: pooled analysis of the RA global clinical trial program over 11 years (cutoff: September 2012) comprising of DANCER (WA17043/U2644g), IMAGE (WA17047/U3373g), MIRROR (WA17044, U2974g), REFLEX (WA17042/IDEC 102-20), SERENE (WA17045/U2973g), SIERRA (U3374g), SUNRISE (U3384g), WA16291, WA16855 (U2653g), WA17531 (IDEC 102-21). **GPA/MPA** • DSR 1048595 Hypogammaglobulinemia in GPA/MPA, dated 9 February 2012; and references therein. • update DSR 1078506 EULAR recommendation to test serum immunoglobulin levels prior to each course of rituximab in GPA/MPA, dated 11 August 2017 • RAVE CSR and RAVE Summary of Clinical Safety. • Study WA27893 (RaVeR) Interim CSR • Study ML22514 (MAINRITSAN) CSR and Summary of Clinical Safety. **Pemphigus Vulgaris** • Study ML22196 CSR and Summary of Clinical Safety. DSR 1080390,(data cut-off date: 15 March 2017) a supplemental Safety Report for Rituximab in Pemphigus and Other Autoimmune Indications.
Risk factors and risk groups	No clear baseline demographic or disease characteristics could be identified to potentially predict occurrence of low Ig concentrations for at least 4 months.

Important identified risk: Hypogammaglobulinemia (non-oncology indications)	
Risk minimization measures	**Routine risk communication:** EU SmPC section 4.4: Special warnings and precautions for use EU SmPC Section 4.8: Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Immunoglobulin levels are recommended to be determined prior to initiating treatment with MabThera. **Other risk minimization measures beyond the Product Information:** *Medicine's legal status:* Medicinal product subject to restricted medical prescription. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	None

Important potential risk: Off-label Use of the Subcutaneous Formulation (NHL and CLL Subcutaneous Formulations)	
Evidence for linking the risk to the medicine	The subcutaneous formulation has only been studied in NHL and CLL populations as stated in the EU SmPC. The potential risk is being monitored via routine pharmacovigilance activities to characterize off-label use of the subcutaneous formulation including the adverse reactions specific to the use of this formulation in unapproved indications. Till now only few cases have been reported where SC formulation has been used for off label indication with no new safety concern.
Risk factors and risk groups	The risks that could be associated with off-label use of the SC formulation also depends on whether the SC formulation is being used for treating a condition for which the rituximab IV formulation is approved (e.g., autoimmune diseases), or diseases for which rituximab IV formulation is also not approved. Furthermore, off-label use is not fully preventable, even with adequate knowledge among healthcare professionals and patients concerning the approved indications.
Risk minimization measures	**Routine risk communication:** SmPC section 4.1 Therapeutic indications Separate EU SmPCs are available for the IV (100 mg and 500 mg) and SC formulations (1400 mg for NHL and 1600 mg for CLL). EU SmPC (for SC formulation) section 4.4: Special warnings and precautions for use EU SmPC (IV and SC) section 4.2: Posology and method of administration **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:* Medicinal product subject to restricted medical prescription **Additional risk minimization measures:** Educational Material for Healthcare Professionals
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Important potential risk: Administration route error (NHL/CLL SC formulations)	
Evidence for linking the risk to the medicine	**Pre-clinical data** Toxicology studies in animals have shown that IV doses of rHuPH20 of greater than 5mg/kg are tolerated without acute harmful effects. Given these findings, acute toxicity from rHuPH20 after IV administration of the SC formulation is not expected in humans. **Clinical data:** During the rituximab SC clinical development program, three patients randomized to the rituximab IV arm were inadvertently administered rituximab SC solution through the intravenous (IV) route. No untoward events were observed in any patient. The three patients seem to have tolerated this overdose via the IV route, as a result of accidental substitution of IV vials by SC vials, without any untoward events. There have been no other known cases of measurable plasma concentrations of rHuPH20 following SC injection in humans or through direct intravenous administration of rHuPH20. Two patients randomized to the SC arm were inadvertently administered rituximab IV via subcutaneous route. No adverse events were associated with error in these patients and remained in the study.[14]. **Safety data:** The reporting rate of administration route error is low. As per the 2017 PBRER (1081698), no serious AEs have been reported as a result of administration route error with Rituximab IV/SC.
Risk factors and risk groups	Administration route error could result from accidental substitution of the SC and IV formulations (e.g., an error in the hospital pharmacy), or incorrect injection technique when using the SC formulation (e.g., placement of the needle directly into a vein or muscle).
Risk minimization measures	**Routine risk communication:** The IV and SC formulations are covered by separate EU SmPCs to reinforce the difference between the IV and SC formulations. EU SmPC (IV and SC) section 1: Name of the Medicinal Product EU SmPC (IV and SC) section 4.2: Posology and method of administration **Routine risk minimization activities recommending specific clinical measures to address the risk:** None. **Other risk minimization measures beyond the Product**

[14] It should be noted that the presentation of Sc and IV vials used in the clinical trials was different from that available commercially. The vials available in the market contain number of safety measures to avoid the potential risk of administration route error

Important potential risk: Administration route error (NHL/CLL SC formulations)	
	Information: *Packaging:* Clear package differentiation • Color differentiation (distinct colored bands) • Unique cap colors for the vials matching the colored bands • Clear statements on both the primary and secondary packaging i.e., words "*subcutaneous*", "*solution for subcutaneous injection*" and "Only *for subcutaneous use*" in red font. Peel-off sticker will be included on the individual vials of the subcutaneous formulations specifying the strength, the route of administration and the indication. SC and IV formulations are covered by separate SmPCs, which include specific warning against incorrect route of administration. *Medicine's legal status*: Medicinal product subject to restricted medical prescription **Additional risk minimization measures:** Educational Material for Healthcare Professionals
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** None

Missing information: Long Term Use In GPA/MPA Patients (GPA/MPA only)	
Evidence for linking the risk to the medicine	There is limited information available on the safety of long term use of rituximab for the treatment of GPA/MPA. The MAH investigated various options to allow collecting long term data from GPA and MPA patients treated with rituximab. In June 2012, the Study WA27893 (RaVeR, US registry) was initiated, and an final report became available in December 2017. Overall, there were no unexpected safety findings in this final analysis of the long-term safety of RTX in the treatment of patients with GPA or MPA who enrolled in this observational study. The safety profile after long-term use (up to 4.32 years and up to 11 courses of RTX) was consistent with the overall safety profile of RTX in autoimmune diseases and the safety profile in patients with GPA/MPA who were treated with RTX for shorter periods of time.
Risk minimization measures	**Routine risk communication:** None **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*: Medicinal product subject to restricted medical prescription. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** RIVAS (BE29950) registry

II.C POST-AUTHORIZATION DEVELOPMENT PLAN

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

None.

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

RIVAS

Purpose of the study: This study is a non-interventional secondary data collection safety study in patients with GPA/MPA exposed to rituximab or other available treatments as part of their standard clinical care. Data will be annually extracted from the Cambridge site within UKIVAS database.