WHO-PQTm SCIENTIFIC DISCUSSION

This part outlines the scientific assessment and knowledge about this product at the time of prequalification. Updates to this information are included in parts 1 to 5 and 8 of this WHOPAR.

Name of the Finished Pharmaceutical Product:	MabThera[1] - 100mg/10mL concentrate for solution for infusion
Manufacturers of Prequalified Product:	Filling of vials, primary packaging: Roche Diagnostics GmbH Sandhofer Straße 116 D-68305 Mannheim Germany Genentech Inc. 1 DNA Way South San Francisco; CA 94080-4990 USA Genentech, Inc. 4625 NE Brookwood Parkway Hillsboro, OR 97124-9332 USA Name and address of the manufacturer responsible for batch release Roche Pharma AG Emil-Barell-Str. 1 D-79639 Grenzach-Wyhlen Germany
Active Pharmaceutical Ingredient (API):	Rituximab
Pharmaco-therapeutic group (ATC Code):	Antineoplastic agent, monoclonal antibody (L01XC02)
WHO recommended therapeutic indications:	diffuse large B-cell lymphoma, chronic lymphocytic leukaemia and follicular lymphoma

1. Introduction

[1] Trade names are not prequalified by WHO. This is the national medicines regulatory authority's responsibility.
Throughout this WHOPAR the proprietary name is given as an example only.

Rituximab is a genetically engineered chimeric mouse/human monoclonal antibody representing a glycosylated immunoglobulin with human IgG1 constant regions and murine light-chain and heavy-chain variable region sequences. The antibody is produced by mammalian (Chinese hamster ovary) cell suspension culture and purified by affinity chromatography and ion exchange, including specific viral inactivation and removal procedures.

The prequalification of this product by the WHO Prequalification Team: Medicines (PQTm) is based on the approval by a stringent regulatory authority (SRA), namely the "European Medicines Agency" (EMA http://www.ema.europa.eu/ema/) in line with the "WHO Guidelines on submission of documentation for the pilot procedure for prequalification of rituximab or trastuzumab approved by stringent regulatory authorities"[2].

Hence, no assessment of the data underlying this approval has been undertaken within PQTm. However, according to the above-mentioned guidelines, WHO requested additional data for the safe use of the product in regions relevant for prequalified products and this information is included in this section of the WHOPAR

2. Assessment of Quality

Product packaging and shipping

The assessment of the packaging and shipping of the product has been done according to the principles laid down in the WHO guidelines on the international packaging and shipping of vaccines (WHO/IVB/05.23), partially applicable also to biotherapeutics.

The Applicant provided data to demonstrate the maintenance of the required 2°C - 8°C exposing the product to a realistic worst case for transportation via air-freight, including road transportation and warehousing & handling. Summer profiles used a temperature of 50°C as the high temperature end that the 2-8°C container and product load were exposed. Furthermore, shipping lane validation was performed to support product transportation from the labeling and packaging site to the warehouses. The shipping lane provided an overall extreme duration scenario for the shipping of the containers. All the validation results met the pre-defined acceptance criteria and the results demonstrate that drug product shipping procedure has been validated, in compliance with WHO requirements.

The Applicant provided evidence to perform 100% temperature monitoring for all shipments. Calibrated monitoring devices are attached to the individual pallets and are used to assess the incoming material. During the assessment by the Applicant, potential temperature excursions during the transport are revealed and the product quality impact is assessed against the stability data of the affected.

The Applicant also provided evidences that the shipping process is based on international regulations from major HAs including WHO Good Distribution Practices for pharmaceutical products as well as Model guidance for the storage and transport of time- and temperature–sensitive pharmaceutical products.

Arrangements for handling complaints and product recalls

The procedure for handling product quality complaints and product recalls submitted by the applicant provides details, among others, on the initial assessment of potential complaint criticality,

[2] https://www.who.int/medicines/regulation/biotherapeutic_products/en/

urgency of actions, root cause investigation process and impact assessment on other batches and/or products, established timeframe for the completion of the investigation process, established timelines for recall notification to National Medicines Regulatory Authorities and WHO, description of the recall arrangements and actions to put in place at the distribution level, as well as description of the periodical mock-recall (including the recommendation to 3rd parties about how to execute, document and report mock recalls).

The applicant confirmed that the handling of complaints and recalls will also be clearly defined in the agreements or contracts between the manufacturer and the procurement agency, which manages the distribution of the medicinal product in LMIC.

Conclusion: the quality part of the dossier is accepted.

Pharmacovigilance - WHO PREQUALIFICATION-SPECIFIC ADDENDUM to the RMP

WHO assessed the latest SRA-approved Risk-Management Plan (RMP) and post-marketing safety reports together with a WHO PQ-specific addendum to the RMP according to the structure detailed on the WHO-PQT website[3]

The WHO-prequalification-specific addendum to the RMP is reported below.

Conclusion: the pharmacovigilance part of the dossier is accepted.

[3] https://www.who.int/medicines/regulation/RMP_AddStructureDec2019-2.pdf?ua=1)

Risk Management Plan Addendum for WHO Prequalification Pilot

MabThera (rituximab) 100 mg and 500 mg

Based on EU RMP Version 21.1

Approval Date: See latest date in date stamps below

Date and Time (UTC)	Reason for Signing	Name
19-Jun-2020 08:18:04	Company Signatory (PV)	Kirchner, Petra (kirchnp1)

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ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
EEA	European Economic Area
EMA	European Medicines Agency
HA	Health Authority
HCP	healthcare professionals
ICSR	individual case study report
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	intravenous
LMIC	Low and Middle Income Countries
NAP	Nationally Approved Product
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
RMP	Risk Management Plan
SRA	Stringent Regulatory Authority

1. INTRODUCTION

1.1 ONCOLOGY INDICATION(S) AND DOSAGE(S) IN THE EUROPEAN ECONOMIC AREA

Detailed information on the following indications and dosages in the European Economic Area (EEA) are provided in the EU Risk Management Plan (RMP) version 21.1, and in the Summary of Product Characteristics:

- Non-Hodgkin's Lymphoma (adult and pediatric patients)
- Chronic Lymphocytic Leukemia (adult patients).

1.2 SUMMARY OF SAFETY CONCERNS

Table 1 Summary of the Safety Concerns, Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern as per EU RMP v21.1

Safety concern	Risk minimization measures	Pharmacovigilance activities
Infections, including serious infections	**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:** *Medicine's legal status:* Medicinal product subject to restricted medical prescription **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities:** None
Progressive Multifocal Leukoencephalopathy	**Routine risk communication:** EU SmPC Section 4.4: Special warnings and precautions for use **Routine risk minimization activities recommending**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Guided Questionnaires

	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 evaluations, including Magnetic Resonance Imaging 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:** None	**Additional pharmacovigilance activities:** None
Hepatitis B Reactivation All Indications	**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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

	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	
Use in Pregnancy and Lactation **All Indications**	**Routine risk communication:** EU SmPC Section 4.6 Fertility, pregnancy and lactation **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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** Standard pregnancy report form for follow-up. **Additional pharmacovigilance activities:** None

HBcAb= Hepatitis B core antibody; HBsAg= Hepatitis B surface antigen; PML= Progressive Multifocal Leukoencephalopathy; SmPC=Summary of Product Characteristics.

1.3 ACKNOWLEDGEMENT FROM APPLICANT

The Applicant acknowledges that the healthcare settings and infrastructure may vary between countries, and that following prequalification, the adequacy of safety concerns, pharmacovigilance (PV) activities, risk minimization measures and traceability of the product at a national level will be evaluated. The Applicant will implement sufficient PV, risk minimization measures, and product traceability following product prequalification even if differences, compared to Stringent Regulatory Authorities (SRAs), in health care settings and/or infrastructure, are found at a national level.

2. SUMMARY OF THE METHODOLOGICAL CONCEPTS THAT WILL BE EMPLOYED AT A NATIONAL LEVEL FOR COUNTRY SPECIFIC RMPS

2.1 SAFETY CONCERNS

Based on assessment of extensive data collected for more than 20 years, and with a cumulative post-marketing exposure of ~ 5,101,756 onco-hematological patients on intravenous (IV) formulation, the safety profile of MabThera is well characterized, and a positive benefit-risk profile is well established in the approved oncology indications.

Before a product enters into a new market in a country, on the basis of either the Core RMP or the EU RMP (depending on the country-specific requirements), the Local Safety Responsible at the Roche Affiliate for the new market country, is responsible for the preparation and implementation of a local RMP. This could be performed, as applicable, in collaboration with other Affiliate functions (e.g., Medical; Local Drug Regulatory Affairs) in order to get a full understanding of the local settings, and based on these, to determine whether the information included in the core or EU RMP (e.g., description of safety concerns; PV activities) is applicable to the local market, and whether there are any potential different or new safety concerns for the country in scope. This step includes the assessment of several specific country factors which vary across countries, and takes into account the current practices where the product is intended for use, such as local healthcare settings, local medical practice and infrastructures, epidemiology, local label. Ultimately, this could result in a local adaptation of the RMP (e.g., including revision and/or description of local specific safety concerns) depending on specific national needs, feasibility and local regulations.

In case there is no Roche Affiliate in a certain country, the tasks/steps described above are conducted by a designated representative in the respective country or by a Roche affiliate in another country with in depth knowledge of the country of intended new launch.

Roche global PV system includes Signal Detection and Management processes which identify, assess and address any potential safety issue in a timely and effective manner to ensure that Roche products' risk profiles are continuously monitored. Signal detection activities are performed at local levels by Local Safety Responsibles based on safety data collected at local level (e.g., individual case study report [ICSR]), as well as by the global drug safety staff in the context of the globally collected data. For each product, a Signal Detection Plan is in place which outlines the events to Monitor, Adverse Events of Special Interest, standard routine signal detection activities, and product-specific signal detection activities. The outcome of the PV activities performed globally and locally could lead to a re-evaluation of the adequacy of the safety information described in the local RMP in place, a potential further revision and local adaptation (which is primarily managed at local level by the Local Safety Responsibles). In addition, the safety profile

of medicines approved locally is also monitored by local Health Authorities, which can request the local affiliates to modify the local RMP and the PV measures in place to address any new identified safety concerns or situations.

2.2 PHARMACOVIGILANCE ACTIVITIES

Roche's global PV system employs a robust and comprehensive process to ensure signal detection, validation, prioritization, and assessment. The process ensures appropriate escalation to the company governance body, in addition to the prompt communication of safety concerns to regulatory authorities, Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs), Investigators, treating physicians, and the public throughout the product lifecycle.

Roche proactively identifies and evaluates potential safety issues from reported adverse events (AEs) and other available safety data and assesses the potential impact of these data on the risk profile of Roche medicinal products. Established routine PV and signal generation activities are used to capture and review safety information, including cases entered onto the Roche Global Safety Database and information retrieved from other sources, including from regulatory authorities.

Signal generation strategies are employed to systematically review safety data, including: Customized Periodic Listings; Standardized periodic case review; Systematic, regular literature searches of internationally recognized biomedical databases; Signal Detection, Assessment and Management Using Disproportionality Analysis; Trending analysis for potential product defects.

Safety data (e.g., AE reports) collected at a national level from the use of Mabthera are also integrated in the global PV system described above to monitor its safe use and to ensure a positive benefit-risk profile based on local practices or specificities of the areas where the product is used. This is also achieved via Affiliate drug safety units in local territories that ensure that safety data relating to the use of Roche drugs are systematically collected to high standards of medical quality, enabling the evaluation of causal relationship, identification of changes of frequency, or a modification of the treated population, as well as managed in accordance with medical ethics and current local regulations. This also includes assessment of any additional PV activities required to address local specificities that may change the benefit-risk profile defined within local settings. Local specificities considered could include epidemiology (e.g., infection), healthcare infrastructure, clinical practice, social, economic and other.

Roche confirms that, the company Affiliate or company representative will establish contact with appropriate PV contact function within the national PV centre (e.g., Ministry of Health) or National Regulatory Authority. In countries where a PV contact function is not present, Roche Affiliate or representative responsible for that particular country, will confirm who the appropriate contact function is to establish contact for PV questions

between company and National Regulatory Authority or other National Health Agency/Organization.

Overall, Mabthera is expected to be used in oncology centers, where other oncology products (e.g., biologics) are also handled and which are expected to follow PV standards.

Additional PV and risk minimization activities, once approved by the EMA or other national competent authority, are considered PV commitments. The overview of adherence to RMP commitments is monitored by two components as outlined below.

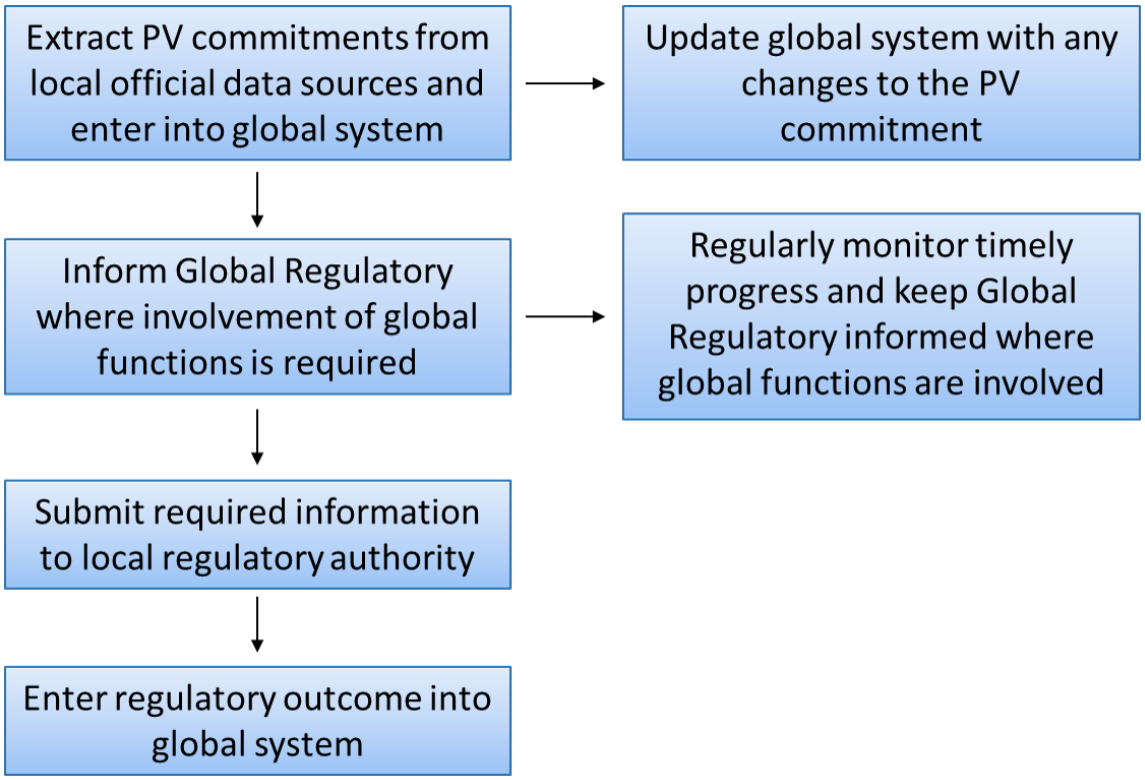
The RMP Implementation Coordinator monitors the local implementation of additional PV and/or risk minimization activities for their assigned countries (or territories) and tracks these in the relevant specific company system. This provides oversight of adherence to Roche-defined submission timelines for additional risk minimization activities. This data is integrated with the product approval and marketing status and a compliance assessment is performed and documented, providing the basis for compliance metrics generated on a monthly timeframe.

All PV commitments are tracked using the relevant system which provides oversight of adherence to Regulatory Authority agreed submission timelines. The process for tracking PV commitments for Nationally Approved Products (NAPs) in EEA countries and all non-EU country-specific requirements is shown in Figure 1.

Depending on requirements, which differ from country to country, Roche Affiliates establish contacts with National Regulatory Authorities, and the RMPs are submitted to the National Regulatory Authorities responsible for their assessment and approval as applicable. In countries without a National Regulatory Authority, the local Affiliates determine the local adaptation and implementation of the core or EU RMP based on local needs, following the assessment described in Section 2.1. In some situations, a “reference” National Regulatory Authoritiy” (e.g., of a neighbouring country), can assess and approve the RMP for a country where no National Regulatory Authority is present.

A Periodic Safety Update Report (PSUR) including an evaluation of all safety data collected globally during the reporting period, is prepared annually (for MabThera, the data-lock point is 17th November). PSURs are submitted in the EU in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. PSURs will be prepared and submitted in accordance with the national requirements.

Figure 1 Tacking PV Commitments for Nationally Approved Products within the EEA Countries and All Non EU Country Specific Commitments



Note: The actions described in Figure 1 are all fulfilled by the appropriate local regulatory manager who has responsibility for the product in question.

2.3 RISK MINIMIZATION MEASURES

The EU RMP for MabThera in hematological malignancy indications entails only routine risk minimization and pharmacovigilance activities. Currently there are no ongoing additional risk minimization activities (e.g., patient or physician education programs) or additional pharmacovigilance activities (e.g., post-authorization safety studies). A description of the important and potential risks and associated routine risk minimization activities are provided below.

Table 2 Risk minimization measures

Important Identified Risks	Routine risk minimization activity	Applicability in LMICs
Infections, including serious infections *Description:* • Immunosuppression caused by Mabthera and chemotherapy agents may predispose patients to an increased risk of a wide range of viral and bacterial infections, including some serious infections. • The product information provides instructions for managing infections in general, as well as for managing PML and HBV reactivation.	**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:** *Medicine's legal status*:	Product information provides clear instructions on prevention, recognition and management of Infections. *Applicability in LMICs* • Secondary infections associated with use of Mabthera occur also in patients receiving chemotherapy without Mabthera, and in conditions such as HIV that cause immunosuppression. Physicians working in oncology centres, and those with experience managing HIV, have experience in recognizing and treating the most common secondary infections associated with immunosuppressants and/or in immunocompromised patients. • Diagnosis and treatment of secondary infections would also depend on the availability of adequate microbiology diagnostic services as well as suitable antibiotics and/or antiviral agents.

	Medicinal product subject to restricted medical prescription	
Progressive Multifocal Leukoencephalopathy *Description* • Rare neurological condition (approx. 8 cases per 100'000 patients treated with Mabthera) caused by reactivation of John Cunningham virus (JCV) • Definitive diagnosis (Berger 2013) requires either: a) histopathology and JCV identified in brain tissue (via in situ hybridization) ***or*** b) clinical and radiological features suggestive of PML and JCV in CSF (via PCR) • As a minimum, brain imaging (MRI) is necessary to exclude other more common neurological disorders that may present with similar symptoms and signs.	**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 Magnetic Resonance Imaging 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**	Product information provides clear instructions on prevention, recognition and management of Progressive Multifocal Leukoencephalopathy . *Applicability in LMICs* • Definitive diagnosis requires availability of histopathology as well as technology for performing JCV in situ hybridization and/or PCR. • If neither MRI nor laboratory facilities for histopathology and JCV testing are available, the diagnosis can still be considered possible or probable based on other clinical evidence. • Although PML is a very rare complication of Mabthera therapy, physicians need to have a high index of suspicion in order to ensure that the diagnosis is made early and that further Mabthera therapy is not given. Of note, PML is a common complication of untreated HIV infection (~5% of patients with HIV who do not receive antiretroviral therapy). Hence, in LMICs with a high prevalence of untreated HIV infection, physicians could be expected to have some knowledge and experience in the diagnosis and management of PML compared to those in other regions.

	Information: *Medicine's legal status:* Medicinal product subject to restricted medical prescription	
Hepatitis B Reactivation *Description* • Mabthera may increase the risk of reactivation of HBV in patients with chronic HBV	**Routine risk communication:** 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**	Product information provides clear instructions on prevention, recognition and management of Hepatitis B reactivation. *Applicability in LMICs* • Chronic HBV has higher prevalence in LMICs than in wealthy countries. Hence, the chance of HBV reactivation may be greater in LMICs, but also the level of knowledge and experience among HCPs recognizing and managing the condition. • Screening and management of HBV should be available in LMICs given its high prevalence, as well as availability of antiviral agents for treatment of HBV infection.

	Information: *Medicine's legal status*: Medicinal product subject to restricted medical prescription.	
Missing Information		
Use in Pregnancy and **Lactation** **All Indications**	**Routine risk communication:** SmPC section 4.6: Fertility, pregnancy and lactation **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.	Product information provides clear instructions on use in pregnant and lactating women *Applicability in LMICs* The product information states clearly that:- • Pregnant patients should not be administered with MabThera unless the possible benefit outweighs the potential risk.. • Women should not breastfeed while treated with MabThera and for 12 months following MabThera treatment.

JCV=John Cunningham Virus; LMICs=low and middle income countries; MRI=magnetic resonance imaging; PML= Progressive multifocal leukoencephalopathy; SmPC=summary of product characteristics.

In general, access to the diagnostic and treatment facilities needed to diagnose and manage patients with lymphoma in low and middle income countries (LMICs) would imply access to the basic diagnostic and treatment facilities that are needed to manage the key risks associated with Mabthera therapy. MabThera is expected to be used in oncology centers with certain standards. Availability of resuscitation facilities is also required for other oncology products (e.g., biologics).

Core or EU RMPs are generally adopted at local level as main reference for risk minimization activities, which can further be adapted depending on several variables across countries (and approved by local regulatory authorities if applicable) as well as revised to add additional risk minimization activity, if required.

Before a new market entry, the Local Safety Responsibles and/or RMP Implementation Coordinators at Affiliates assess the adequacy of the safety concerns, PV activities and risk minimization activities described in the core or EU RMP, approved by SRAs, or whether a revision is required depending on local settings in order to address potential specific national needs (see also Section 2.1). This evaluation for local adaptation, can be performed with the involvement from different functions, as applicable, at Affiliates (e.g., Medical; Local Drug Regulatory Affairs) to get a comprehensive understanding of the country settings.

For this purpose, several key elements of the country settings are taken into account such as the local medical practice, including how familiar the healthcare professionals are with the product, local regulations, local technical language, target audience in the country, local healthcare system and infrastructure including the local healthcare delivery system of the product, and local label.

In the perspective of ensuring the risk minimization activities fit the local healthcare system and adherence to treatment behavior guideline, the RMP Implementation Coordinator verifies the adherence to the local requirements, and a Compliance officer ensures the adherence to additional monitoring requirements and non-promotional content. If needed, each risk minimization activity is then expected to be adapted to local needs to ensure it is tailored for the local market. This could include for instance addition to the local label of specific guidance for the healthcare professionals (HCPs) or specific requirements to be in place as routine or additional risk minimization activities.

MabThera product information (e.g., Summary of Product Characteristics/package leaflet) provides HCPs and patients with the essential information on how MabThera should be used, including routine risk minimization activities. Product label is available on public websites such as EMA and FDA websites, and could also be available on local authority websites.

The MabThera label also includes instructions for it to be used under close supervision by an experienced HCP in an environment where full resuscitation facilities are immediately available. Local company representatives in contact with local HCPs ensure this is appropriately communicated. If deemed necessary, additional locally developed documents, e.g., checklists, can be used to inform and train HCPs about the correct use of MabThera and the risk minimization requirements.

Additional information, e.g., on the safe use of MabThera, is also provided on the Roche website, accessible in all countries. When required, non-promotional product education material can be provided by Roche local staff on field to ensure HCPs are adequately informed and trained about the product. In addition, HCPs have the opportunity to directly contact responsible local affiliate for their country for inquiries.

Information on how Roche monitors whether the risk minimization activities are being implemented has been included within Section 2. The effectiveness of routine risk minimization activities at local level is generally monitored by the frequency (spontaneous reporting rates) and/or severity of an adverse reaction at local level in relation to patients' exposure via signal detection activities, which provides an overall measure of the level of risk control that has been achieved with any risk minimization activity in place.

For additional PV and/or risk minimization activities, effectiveness measures are also typically monitored by "Process indicators", i.e., measures of the extent of implementation (e.g., distribution records of risk minimization material), which are tracked and recorded by local affiliates via specific Roche internal systems. The actual success rate is calculated based on the success assessment criteria customized by each affiliate and determined in advance for the methods of distribution. In case the actual success rate is lower than the predefined target success rate, appropriate actions are taken as defined in the local implementation strategy or could be discussed directly with the local HA if applicable. In rare instances, a local HA can request a local study to be conducted locally to assess the effectiveness of risk minimization activities. In general, it is expected that these studies are multi-country studies and are operated by the global functions.

2.4 PRODUCT TRACEABILITY

Roche ensures traceability using an electronic system which covers the entire Roche supply chain for our finished products up to delivery to the first tier customers (i.e., first party outside of Roche). Traceability beyond this point is under the responsibility of the customer. This responsibility is emphasized under the Roche Quality Exhibit, which is an integral part of the purchasing agreement with the customer. Roche applies the same standardized procedure to all external customer deliveries globally and acknowledges the varying levels of infrastructure among them. In order to manage this, we are supporting our first tier customers globally, e.g. with

- additional written guidance, for instance in performing Mock Recalls
- Roche-organized face to face trainings targeted to our customers as well as part of industry peer group initiatives (e.g., Rx360 educational stream)
- an established, focused global supply chain and affiliate quality organization. This includes sub-regional quality managers within the regions, who work closely with the local customers, e.g., by cutting out language barriers and being available for face to face interactions

Further Roche is driving initiatives to simplify the distribution chain in order to reach the patient faster by reducing the number of intermediaries.

For AE reports, if either the trade name or batch number is missing from the initial reports, follow-up requests are initiated to request this information from the reporter. These follow-up attempts are documented, and if the reporter is unwilling or unable to provide the missing

information, this is also documented within the case. For any case reported with generic drug rituximab, the case processors are therefore trained to raise follow up queries to obtain from the reporter the trade name and batch number. Once received, this information is captured in the AE report.

In addition, to ensure recording by the healthcare professionals of the trade name and batch number, the MabThera product information/label includes a warning that the tradename and batch number of the administered product should be clearly recorded in order to improve traceability of biological medicinal products

3. REFERENCES

Berger et al. PML diagnostic criteria consensus statement from the AAN neuroinfectious disease section. Neurology 2013; 80: 1430-8