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:	Rixathon [1] - 100mg/10mL concentrate for solution for infusion
Manufacturers of Prequalified Product:	Name and address of the manufacturer(s) of the biological active substance(s) Sandoz GmbH Schaftenau Biochemiestr. 10 6336 Langkampfen AUSTRIA Boehringer Ingelheim Pharma GmbH & Co. KG Birkendorfer Straße 65 88397 Biberach an der Riss Germany Name and address of the manufacturer(s) responsible for batch release Sandoz GmbH Schaftenau Biochemiestr. 10 6336 Langkampfen AUSTRIA Lek Pharmaceuticals d.d. Ljubljana Verovškova 57 1526 Ljubljana Slovenia
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] 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.

1. Introduction

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. A transport category is assigned for all product shipment based on available stability data. This category includes consideration on the transport condition and any tolerated temperature excursions during transport. Any deviation from the set transport category would trigger a deviation, which results in a detailed evaluation and assessment of the deviation by subject matter experts. Further release of a shipment that is affected by a temperature deviation depends on the outcome and conclusions of these investigations and can only happen if any potential impact on product quality can be excluded based on the available stability data. The applicant provided also evidences that provisions are in place to ensure that the containers are stored in cold storage areas and/or connected to electrical power in case of any delays in transportation. 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 also evidences that all routine international shipments are monitored using calibrated temperature data loggers. Shipments within the countries are performed either with temperature-controlled cars or within qualified shipment containers. In both cases, the temperature is constantly monitored by qualified systems.

Finally the applicant confirmed that the distribution chain under the applicant responsibility reaches the final destination.

Arrangements for handling complaints and product recalls

The Applicant provided a description of the complaints and recall process. The established working procedures ensure that any complaint is communicated in a timely manner and via pre-defined

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

channels to the manufacturing site that is responsible to perform the investigation. After completion of the investigation and if necessary appropriate definition of CAPA, the customer is informed via the country organization of the investigation outcome.

Furthermore, the Applicant provided details of the established comprehensive escalation, incident management and market action processes on a global level with related procedures and tools in place for product recalls. Any incident that could result in a market action is being identified and escalated following the clearly defined process.

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.

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)

SANDOZ A Novartis Division

Chief Medical Office & Patient Safety

Rituximab (Rixathon®, GP2013)
100 mg and 500 mg
Concentrate for solution for infusion

722-0133-970-WHO-PQ specific RMP addendum-4-0

Rixathon® - WHO-PQ specific RMP addendum

Author(s):	Sandoz
Date:	03-Apr-2023
Replaces:	Version 3.0
Number of pages:	21

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List of abbreviations

ADR	Adverse drug reaction
AE	Adverse Event
ARTIS	Anti-Rheumatic Therapy in Sweden
BSRBR	British Society of Rheumatology Biologics Register
BTP	Biotherapeutic product
CD20	B lymphocyte antigen CD20
CHOP	Cyclophosphamide, doxorubicin, vincristine, prednisolone
CDS	Core Data Sheet
CLL	Chronic lymphocytic leukemia
DLBCL	Diffuse large B-cell lymphoma
EMA	European Medicines Agency
EU	European Union
FL	Follicular lymphoma
GPA	Granulomatosis with polyangiitis
GVP	Good Pharmacovigilance Practice
HA	Health Authority
HCP	Health Care Professional
IRR	Infusion related reactions
IV	Intravenous
MAH	Marketing Authorization Holder
MPA	Microscopic polyangiitis
NMRA	National Medicines Regulatory Authority
NHL	Non-Hodgkin’s lymphoma
PCP	Pneumocystis jirovecii pneumonia
PI	Patient Information
PL	Patient Leaflet
PML	Progressive multifocal leukoencephalopathy
PQ	Prequalification
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
QPPV	Qualified Person Responsible For Pharmacovigilance
RA	Rheumatoid Arthritis
RABBIT	Rheumatoide Arthritis: Beobachtung der Biologika-Therapie
RMP	Risk Management Plan
RMM	Risk minimization measure
SmPC	Summary of Product Characteristics
SRA	Stringent Regulatory Authority
UK	United Kingdom
US	United States
WHO	World Health Organization

1 Introduction

This document serves as World Health Organization (WHO) Prequalification (PQ) specific addendum to the European Safety Risk Management Plan (EU RMP), for seeking approval from participating individual National Medicines Regulatory Authorities (NMRA) via WHO collaborative procedure and will be effective upon prequalification of Rixathon®.

1.1 Invited indications

The WHO invitation for product evaluation of the rituximab product Rixathon® within the prequalification pilot procedure includes the following indications in adults:

- Diffuse large B-cell lymphoma (DLBCL)
- Chronic lymphocytic leukemia (CLL)
- Follicular lymphoma (FL)

1.2 Posology

Rituximab should be administered under close supervision of an experienced healthcare professional, and in an environment where full resuscitation facilities are immediately available (see section 4.2 of the EU SmPC).

Premedication and prophylactic medications

Premedication consisting of an anti-pyretic and an antihistaminic, e.g. paracetamol and diphenhydramine, should always be given before each administration of rituximab.

If rituximab is not given in combination with glucocorticoid-containing chemotherapy, glucocorticoids should be considered.

For patients administered rituximab according to the 90-minute infusion rate, premedication with glucocorticoids should be considered if rituximab is not given in combination with glucocorticoid-containing chemotherapy.

Prophylaxis with adequate hydration and administration of uricostatics starting 48 hours prior to start of therapy is recommended for CLL patients to reduce the risk of tumor lysis syndrome. For CLL patients whose lymphocyte counts are > 25 x 10^9/L it is recommended to administer prednisone/prednisolone 100 mg intravenous shortly before infusion with Rituximab to decrease the rate and severity of acute infusion reactions and/or cytokine release syndrome.

Posology

It is important to check the medicinal product labels to ensure that the appropriate formulation is being given to the patient, as prescribed.

Non-Hodgkin's lymphoma

Follicular non-Hodgkin's lymphoma

Combination therapy

The recommended dose of rituximab in combination with chemotherapy for induction treatment of previously untreated or relapsed/ refractory patients with follicular lymphoma is: 375 mg/m^2 body surface area per cycle, for up to 8 cycles.

Rituximab should be administered on day 1 of each chemotherapy cycle, after intravenous administration of the glucocorticoid component of the chemotherapy if applicable.

Maintenance therapy

- Previously untreated follicular lymphoma

The recommended dose of rituximab used as a maintenance treatment for patients with previously untreated follicular lymphoma who have responded to induction treatment is: 375 mg/m^2 body surface area once every 2 months (starting 2 months after the last dose of induction therapy) until disease progression or for a maximum period of two years. (12 infusions in total)

- Relapsed/refractory follicular lymphoma

The recommended dose of rituximab used as a maintenance treatment for patients with relapsed/refractory follicular lymphoma who have responded to induction treatment is: 375 mg/m^2 body surface area once every 3 months (starting 3 months after the last dose of induction therapy) until disease progression or for a maximum period of two years. (8 infusions in total)

Monotherapy

- Relapsed/refractory follicular lymphoma

The recommended dose of rituximab monotherapy used as induction treatment for adult patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy is: 375 mg/m^2 body surface area, administered as an intravenous infusion once weekly for four weeks.

For retreatment with rituximab monotherapy for patients who have responded to previous treatment with rituximab monotherapy for relapsed/refractory follicular lymphoma, the recommended dose is: 375 mg/m^2 body surface area, administered as an intravenous infusion once weekly for four weeks (see section 5.1 of the SmPC).

Diffuse large B cell non-Hodgkin's lymphoma

Rituximab should be used in combination with CHOP chemotherapy. The recommended dosage is 375 mg/m^2 body surface area, administered on day 1 of each chemotherapy cycle for 8 cycles after intravenous infusion of the glucocorticoid component of CHOP. Safety and efficacy of rituximab have not been established in combination with other chemotherapies in diffuse large B cell non- Hodgkin’s lymphoma.

Dose adjustments during treatment

No dose reductions of rituximab are recommended. When rituximab is given in combination with chemotherapy, standard dose reductions for the chemotherapeutic medicinal products should be applied.

Chronic lymphocytic leukemia

The recommended dosage of rituximab in combination with chemotherapy for previously untreated and relapsed/refractory patients is 375 mg/m^2 body surface area administered on day 0 of the first treatment cycle followed by 500 mg/m^2 body surface area administered on day 1

of each subsequent cycle for 6 cycles in total. The chemotherapy should be given after rituximab infusion.

Elderly

No dose adjustment is required in elderly patients (aged >65 years).

Method of administration

The prepared rituximab solution should be administered as an intravenous infusion through a dedicated line. It should not be administered as an intravenous push or bolus.

Patients should be closely monitored for the onset of cytokine release syndrome (see section 4.2 of the EU SmPC). Patients who develop evidence of severe reactions, especially severe dyspnoea, bronchospasm or hypoxia should have the infusion interrupted immediately. Patients with non-Hodgkin's lymphoma should then be evaluated for evidence of tumor lysis syndrome including appropriate laboratory tests and, for pulmonary infiltration, with a chest X-ray. In all patients, the infusion should not be restarted until complete resolution of all symptoms, and normalization of laboratory values and chest X-ray findings. At this time, the infusion can be initially resumed at not more than one-half the previous rate. If the same severe adverse reactions occur for a second time, the decision to stop the treatment should be seriously considered on a case-by-case basis.

Mild or moderate IRR (section 4.8 of the EU SmPC) usually respond to a reduction in the rate of infusion. The infusion rate may be increased upon improvement of symptoms.

First infusion

The recommended initial rate for infusion is 50 mg/h; after the first 30 minutes, it can be escalated in 50 mg/h increments every 30 minutes, to a maximum of 400 mg/h.

Subsequent infusions

Subsequent doses of rituximab can be infused at an initial rate of 100 mg/h, and increased by 100 mg/h increments at 30 minutes - intervals, to a maximum of 400 mg/h.

If patients did not experience a Grade 3 or 4 infusion-related adverse event during Cycle 1, a 90-minute infusion can be administered in Cycle 2 with a glucocorticoid-containing chemotherapy regimen. Initiate at a rate of 20% of the total dose given in the first 30 minutes and the remaining 80% of the total dose given over the next 60 minutes. If the 90-minute infusion is tolerated in Cycle 2, the same rate can be used when administering the remainder of the treatment regimen (through Cycle 6 or 8).

Patients who have clinically significant cardiovascular disease, including arrhythmias, or previous serious infusion reactions to any prior biologic therapy or to rituximab, should not be administered the more rapid infusion.

1.3 Summary of safety concerns, respective risk minimization measures and pharmacovigilance activities as per Rixathon EU RMP v7.1

Following is the tabulated summary of safety concerns, respective Risk Minimization Measures (RMM) and Pharmacovigilance (PV) activities related to the WHO invited indications. This table reflects the risk profile for the invited indications as described in the EU RMP v7.1 that was compiled based on internal and external global product safety data assessed in totality.

Table 1-1 Tabulated summary of safety concerns and respective RMM and PV activities for WHO invited indications as per Rixathon® EU RMP v7.1

Category	Safety concern	Risk minimization measures (RMM)			Pharmacovigilance (PV) activities	
		Routine RMM	Legal status	Additional RMM	Routine PV activities beyond adverse reactions reporting and signal detection:	Additional PV activities
Important identified risks	Infections (including serious infections)	SmPC sections 4.3, 4.4 and 4.8; section 4.4 where recommendation for exercising caution when considering the use of rituximab in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection is included PL sections 2 and 4	Prescription only	None	None	None

Category	Safety concern	Risk minimization measures (RMM)			Pharmacovigilance (PV) activities	
		Routine RMM	**Legal status**	**Additional RMM**	**Routine PV activities beyond adverse reactions reporting and signal detection:**	**Additional PV activities**
	PML	SmPC sections 4.3, 4.4 and 4.8; section 4.4 where recommendation for monitoring of patients at regular intervals and suspension of further dosing if PML is suspected, considering further evaluation and permanently discontinuing dosing of Rixathon if a patient develops PML is included PL section 4	Prescription only	None	Targeted follow-up questionnaire	None
	HBV reactivation	SmPC sections 4.4 and 4.8; section 4.4 where recommendation for HBV screening before initiation of treatment with Rixathon is included; PL sections 2 and 4	Prescription only	None	Targeted follow-up questionnaire	None
Important potential risks						
	Administration route error	SmPC section 4.2 PL section 3	Prescription only	HCP alert card	None	None

Category	Safety concern	Risk minimization measures (RMM)			Pharmacovigilance (PV) activities	
		Routine RMM	**Legal status**	**Additional RMM**	**Routine PV activities beyond adverse reactions reporting and signal detection:**	**Additional PV activities**
		The outer carton as well as the vial label of the product states: “For intravenous use after dilution”				

2 Summary of the methodological concepts that will be employed at a national level for country specific RMPs

2.1 Safety concerns

2.1.1 Basis for risk profile - Global process of safety signal detection

The MAH uses a combination of internal and external safety data. Qualitative and quantitative safety signal detection approaches are applied in traditional and automated methods.

Traditional signal detection is done across a matrix team through analysis of safety information from different sources. These include

- worldwide safety cases,
- abnormal lab findings/other tests,
- class effects,
- pre-clinical/clinical study findings,
- health authority requests and/or health authority publications,
- medical literature,
- product technical complaints,
- label changes to the reference product / originator and
- screening of specific health authority websites for changes in reference safety information.

The global screening of reference product labeling, health authority websites and medical literature already starts before first marketing authorization, i.e. during the biosimilar development.

The totality of sources for signal detection is thus comprised of information exchanged by local country organizations and the global organization. A further basis for the MAH's RMP is the reference product's RMP, which reflects the longest market experience in terms of patient safety of that product.

Sandoz also performs an automated data mining and signal detection on aggregate individual case safety reports. Spontaneous single cases from all countries are combined, and signal detection based upon designated medical events, disproportionality analysis and increased frequency analysis is performed on a scheduled basis. "Hits" generated by this automated signal detection are then reviewed by global cross-matrix Safety teams. Whilst automated signal detection is not performed at a "country of reporting level", when reviewing the signal the Safety team does assess factors such as country of origin of the signal.

2.1.2 Specific national approaches to identify additional safety concerns

Upon prequalification and before new market entry, Sandoz will undertake an assessment at a national level to identify any potential new safety concerns based on local practices or specificities in comparison to the EU setting (i.e. for example evaluation of local healthcare settings and practice, infrastructure and epidemiology etc.).

Based on this evaluation, any newly identified safety concerns, compared to the EU RMP, will be adequately addressed by implementing appropriate RMMs and/or PV activities either in the country specific RMP annex and/or by revising the EU-RMP, if applicable. Additionally, single cases from patients and health care professionals (HCPs) are received and processed by a team of Pharmacovigilance (PV) professionals working at a regional or national level. This PV team works closely with the concerned country regulatory, medical and product quality teams among others to ensure compliance with local pharmacovigilance regulations, support of local patients and HCPs and the appropriate supply of medicinal products.

The local PV team is responsible for the receipt and data entry into the Sandoz global database of reported adverse events, including all adverse events with an associated product quality complaint. The local PV team therefore oversees all AE reports (including those associated with product quality complaints) at the country level and is also responsible for reporting to the NMRA HA per country specific regulations.

Moreover, the country specific labeling safety changes are implemented in the country specific label according to the NMRA requirements. Local safety labeling change requests received from NMRA that are not yet included in the current core safety information in the Core Data Sheet (CDS) are forwarded to the global safety label management and regulatory groups for further consideration on revising the global CDS.

The MAH periodically checks national and regional NMRA websites for new potential safety signals. Local safety labeling change requests received from national health authorities that are not yet included in the current core safety information in the Core Data Sheet (CDS) are forwarded to the global safety label management and regulatory groups for further consideration on revising the global CDS. The country specific labeling safety changes are implemented in the country specific label according to the national regulatory requirements.

Potential new safety concerns/safety signals identified by the health authority are also raised to the applicant via different safety compliance reporting mechanisms (e.g. RMP or PSUR revision) and addressed accordingly.

2.2 Risk Management System

The MAH efficiently conducts a risk management system worldwide that includes worldwide adverse event reporting, risk identification, pharmacovigilance measures to collect further data on such risks and appropriate risk minimization measures. The risk management system is part of the Novartis Pharmacovigilance System Master File (on file and provided on request).

An approved EU RMP is communicated by the MAH to all worldwide Sandoz/Novartis country organizations. The national implementation of any additional pharmacovigilance and risk minimization measures (if they exist) is done worldwide, including those countries participating in the WHO collaborative procedure, according to the NMRA regulations/requirements.

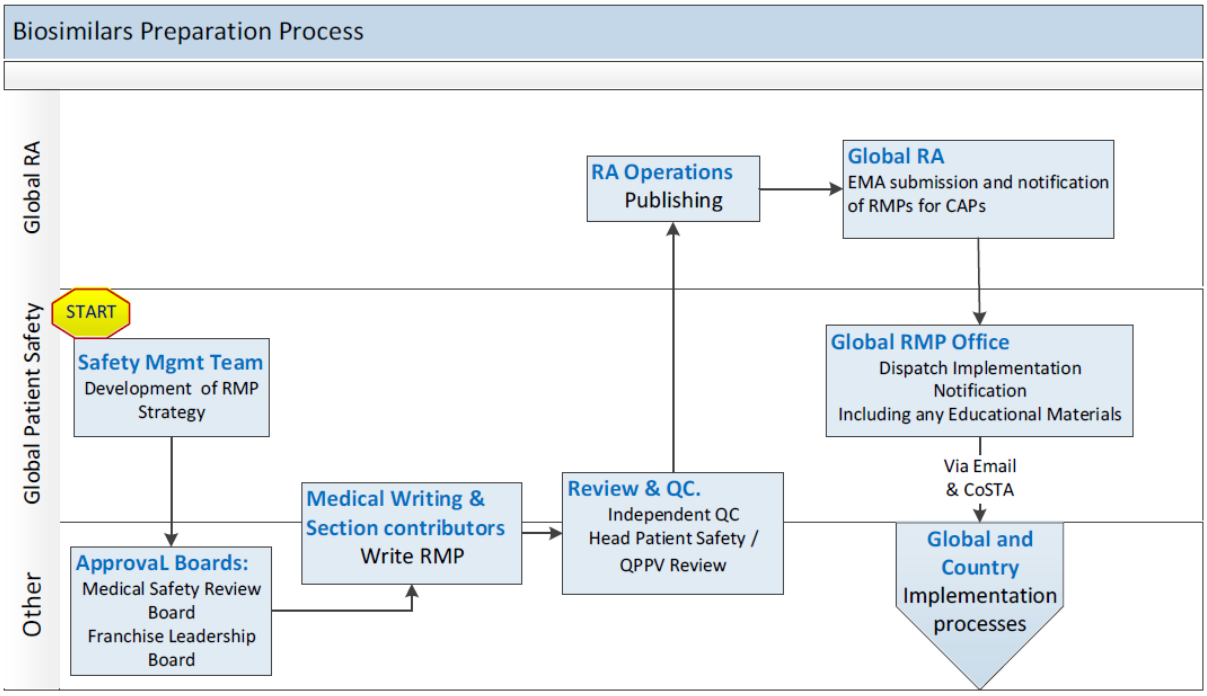
Additionally, before new market entry, local specificities will be considered for the assessment of a need for additional PV activities or additional RMM, compared to those listed in Table 1-1, covering local epidemiology (e.g. infection), healthcare infrastructure, clinical practice, social and economic status, etc., as appropriate. All PV activities or RMM will be implemented as appropriate.

In certain individual countries, e.g. Ghana, where a country-specific EU RMP – addendum is required by the NMRA, this is prepared according to those needs in collaboration of the MAH's global and local sites and implemented nationally. A country-specific EU RMP - addendum will be included in the dossier for national registration of the medicinal product if applicable by local regulation. It may contain differences in the RMP strategy (risks, risk minimization activities, pharmacovigilance activities) as established based on the local assessment and recommended by the NMRA. Furthermore, specific local RMP displays and specific RMM – templates are in use. Any local differences in the RMP strategy are fed back to the applicant's global oversight.

Implementation of RMP is monitored by a local RMP responsible person in each country and all RMP commitments are tracked in the purpose-built RMP Commitment Database (CoSTA – Commitment Status Tracking Application) with oversight locally and at the applicant's global team. Any implementation issues raised by the countries are addressed adequately. All activities are also well defined in the MAH's internal policies.

Figure 2-1 presents an overview on the information and communication flow within Sandoz/Novartis and with health authority to implement the RMP in each country where marketing authorization is sought. The applicant confirms that no marketing authorization will be sought in countries for which no contact with a local health authority for registration or any other adequate contact point is available.

Figure 2-1 Workflow for the RMP preparation process



2.3 Pharmacovigilance activities

2.3.1 Routine pharmacovigilance activities

The Global Pharmacovigilance System ensures that pharmacovigilance obligations are put in place to adequately comply with the regional and national legislations. The Pharmacovigilance System Master File describes all pharmacovigilance activities performed by the MAH in order to ensure compliance with the regional and national legal requirements and safety of its products.

In line with the MAH's policies and global pharmacovigilance legislations, each employee of the MAH as well as any involved service provider as applicable are trained on adverse event reporting obligations. This ensures appropriate case collection, processing, follow up and expediting within Novartis which is followed by adverse event expediting to worldwide health authorities according to local and regional legislations.

Each applicable individual local health authority requirement is adhered, e.g. stricter submission requirements of adverse drug reactions (ADRs), for instance in Uganda where just suspected product and adverse event are already qualifying for an expedite case, or additional case follow up activities beyond the mandatory requirements set up by the company, e.g. in Switzerland, China or Taiwan, are in place.

Measures will be taken in individual countries in cooperation with the local partner, local health authority, HCPs and other relevant organizations to improve drug safety awareness and to promote adverse event reporting from HCPs, Consumers, etc.

2.3.2 Routine pharmacovigilance activities beyond ADRs reporting and signal detection

Periodic Safety Update Reports (PSURs)

The PSUR presents a comprehensive and critical analysis of the risk-benefit balance of rituximab, taking into account new or emerging safety information in the context of cumulative information on risks and benefits. According to the list of European Union reference dates and frequency of submission of PSURs, PSURs for rituximab are written annually by the MAH and are submitted in accordance with the national requirements.

Specific adverse reaction follow-up questionnaires for PML, HBV reactivation:

Specific adverse reaction follow-up questionnaires are provided to the reporters in order to obtain structured information on reported suspected adverse reactions of special interest to further characterize the nature of events, demographics of patients at risk, and the presence of risk factors and confounding factors.

Other forms of routine pharmacovigilance activities for all included risks and missing information:

Follow up of case reports: The minimum desired case information for rituximab includes the brand name and batch number of the suspect product. Additional efforts must be made to collect this information in accordance with GVP Module VI.

2.3.3 Additional pharmacovigilance activities

Before new market entry, local specificities will be considered for the assessment of a need for additional PV activities will cover epidemiology (e.g. infection), healthcare infrastructure, clinical practice, social and economic conditions,... etc. as appropriate to determine if additional PV activities are necessary compared to those listed in the EU-RMP.

Furthermore, the MAH periodically checks national and regional Health Authority websites for new urgent safety measures and conducts regulatory intelligence to verify and to subsequently implement any new/modified local/regional PV legislation, which could imply additional PV activities. Safety data collected internally is periodically assessed in order to determine any applicable actions to address specific safety concerns for particular country/ies or globally.

2.4 Risk minimization measures

2.4.1 Routine risk minimization measures

Routine risk minimization activities, i.e. those which apply to all medicinal products like the SmPC / PI / PL, the labelling (e.g. on inner and outer carton), pack size, the prescription status of the product, are appropriately implemented according to the individual NMRA requirements.

The PI, which is a regulatory relevant document in the majority of low- and middle- income countries, contains robust product information and is considered the relevant information

for HCPs and patients. Furthermore, the package leaflet with relevant safety information is always included in the packaged medicinal product. The MAH ensures marketing the proposed drug product only in countries where implementation of instructions in the label are possible to protect the patients' safety.

Following are few examples of important safety information mentioned in the global core data sheet, which is the basis for national labels

- Rituximab should only be administered under the close supervision of an experienced HCP and in an environment where full resuscitation facilities are immediately available.
- Instructions to closely monitor patients for defined medical conditions are given, e.g. for the onset of cytokine release syndrome, with descriptions of symptoms and advices for the appropriate management of such conditions to help HCPs to better understand manage them appropriately.
- PML, e.g. instructions to HCP about frequency of occurrence, symptoms and course of PML, need for regular monitoring for signs of PML, what to do in case of symptoms being suggestive of PML, what to do in case of diagnosed PML.
- Hepatitis B, e.g. instructions to HCP regarding necessary screening before initiating therapy, no treatment in patients with active hepatitis, measures to avoid hepatitis B reactivation, conditions of patients having developed hepatitis B reactivation.
- Infusion-related reactions (IRR), e.g. symptoms, course of IRR with repeated rituximab infusions, instructions for monitoring of patients with pre-existing cardiac conditions, instructions for interventions at occurrence of IRRs, the need to have medicinal products available for the treatment of hypersensitivity reactions, e.g. epinephrine (adrenaline), antihistamines and glucocorticoids, for immediate use in the event of an allergic reaction during administration of rituximab.

2.4.2 Additional risk minimization measures

Additional risk minimization activities are introduced when they are deemed to be essential for the safe and effective use of the medicinal product.

Beyond information outlined in the label, the current EU RMP v7.1 contains additional risk minimization measures (as per Table 1-1), i.e. HCP alert card, for the important potential risk ‘Administration route error’, which is implemented worldwide via the RMP, including countries participating in the WHO collaborative procedure. At this time, no other safety concern was identified that requires an additional RMM.

The need for additional RMM in a country will be detected by the MAH based on the assessment of the different safety sources (e.g. aggregated data such as PSURs, literature screening, etc.) or by national Health authorities in response to a particular safety signal or concern.

Upon assessment, taking into consideration how familiar health care professionals are with the product, local clinical practice and health care setting/infrastructure, Sandoz will implement, if considered necessary, additional RMM, for example non-promotional

educational material, at the national level. This process could be supported by a checklist for each of the safety concerns and the proposed actions that may be required.

In case, any country-specific RMM is deemed necessary, it will be implemented and described in local working procedures of the applicable countries. In some countries the implementation of RMMs is done by local partners which is governed by a respective local pharmacovigilance agreement.

Sandoz will ensure healthcare professionals have access to the SmPC/PI and where applicable, non-promotional education material are provided to educate that Rixathon should be used only where there are adequate facilities to implement the RMMs for example, close supervision by an experienced HCP is required in an environment where full resuscitation facilities are immediately available.

The MAH has processes and control systems in place to monitor and ensure that SmPCs and non-promotional educational materials are provided to the applicable target audiences, such as HCPs. Furthermore, in some countries SmPC and educational materials are publicly available, e.g. on local HA web sites for continuous access by the HCPs.

To reach the target audience, appropriate materials, methods and channels will be set up in each country. Educational materials can be distributed physically, e.g. during face-to-face meetings with the HCPs, or via certified post, or electronically via emails or public web sites etc. The mechanism of communication and distribution is selected and properly documented by each MAH function considering the specific country market conditions and local national requirements. If applicable, distribution strategies are aligned with the local health authorities.

Please, also refer to Section 2.2 Risk Management System.

2.5 Product traceability

Product traceability is an integral part of Novartis Quality Manual, which is the highest-level Quality governance document at Novartis and applies to all Novartis unites and sites. Specific processes that secure product traceability for Novartis products, including Rixathon, are described in detail in documents such as Global Operating Procedures and Standard Operating Procedures. In addition, compliance with national product traceability requirements is regularly checked by internal Novartis audits and by external HA inspections.

During the manufacturing, a specific lot number is given to each batch of product for identification of the drug substance and drug product. This allows Sandoz to track each drug product batch from manufacturing to distribution and to the final delivery site, such as procurement agencies, clinics or hospitals. As long as the batch number is documented at the final destined hospital, the product can be traced.

Container closure labeling of the product includes the product name, batch number, manufacturer and expiry date of the particular drug product batch, enabling HCPs to record relevant traceability information in the patient file and while reporting the individual case safety reports. In addition, product information will be provided in the tertiary packaging.

The collection of the brand name and batch number is mandatory for all biological products according to GVP requirements. Individual country labels are based on the global core data sheet (CDS), which emphasizes the traceability requirement in *"Special warnings and precautions for use"* section by instructing HCPs to record tradename and batch number of the administered product in the patient file.

> "*In order to improve traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded."*

Sandoz will emphasize the importance of providing the tradename and batch number when reporting suspected adverse reactions in order to ensure recording of this information in the patient's file. Sandoz PV processes are in place to ensure requests are made, including follow-up steps, if required, to obtain the batch number associated with all AE reports for biologic products. Global and local forms used to collect adverse event reports contain mandatory fields for brand name and batch number. If this information was not initially provided, a mandatory follow-up is performed to identify the brand name and batch number(s). Please note that batch number and brand name are a specific request in each targeted follow-up questionnaire included in the EU RMP of rituximab. Based on collected brand name and batch information, national and global signal management is conducted.

If necessary, product traceability system for rituximab can be amended in accordance with the NMRA requirements, after prequalification.

Although countries participating in the WHO collaborative procedure may have different healthcare settings/infrastructure compared to EU, rituximab is prescribed and administered via intravenous infusion by a HCP in a hospital setting. Hence, Sandoz believes, product traceability will be feasible for rituximab, as the distribution channel ends at a hospital.

3 Conclusion

Sandoz acknowledges healthcare settings and infrastructure may vary between countries, and following prequalification, will evaluate the adequacy of the safety concerns, PV activities, RMMs and traceability of the product at a national level. Subsequently, Sandoz will implement sufficient pharmacovigilance, RMMs and product traceability following product prequalification even if differences, compared to SRAs, in healthcare settings and/or infrastructure are found at a nation