EU Risk Management Plan for Ituxredi (Rituximab)

RMP version to be assessed as part of this application:

RMP Version number:	1.1
Data lock point for this RMP:	22 May 2025
Date of final sign off:	05 June 2025
Rationale for submitting an updated RMP:	Response to EMA assessment report, to update the RMP to align it with reference product RMP
Summary of significant changes in this RMP:	Following changes made: Part II: SIV.1 - Table 2 updated to align with reference product RMP - In Table 2, Criterion for "Fertile men or women of childbearing potential not using adequate contraception (oral contraceptives, intrauterine device or barrier method of contraception in conjunction with spermicidal jelly or surgically sterile). Pregnant or breastfeeding women" is updated
Other RMP versions under evaluation:	Not applicable

Details of the currently approved RMP:

Version number: 0.4

Approved with procedure: 19 September 2024 (EMEA/H/C/6224)

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Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) **(INN or common name)**	Rituximab
Pharmacotherapeutic group(s) (ATC Code)	Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibody. ATC code: L01FA01
Marketing Authorisation <Holder> <Applicant>	Reddy Holding GmbH
Medicinal products to which this RMP refers	02
Invented name(s) in the European Economic Area (EEA)	Ituxredi 100 mg Ituxredi 500 mg (Hereafter referred to as Ituxredi)
Marketing authorisation procedure	Centralised procedure - EMEA/H/C/6224
Brief description of the product	Chemical class Chimeric mouse/human monoclonal antibody.
	Summary of mode of action Rituximab binds specifically to the transmembrane antigen, cluster of differentiation (CD)20.. The CD20 antigen is expressed on > 95% of all B-cell non-Hodgkin's lymphomas (NHL). The Fab domain of rituximab binds to the CD20 antigen on B lymphocytes and the Fc domain can recruit immune effector functions to mediate B cell lysis. Possible mechanisms of effector-mediated cell lysis include complement-dependent cytotoxicity (CDC) resulting from C1q binding, and antibody-dependent cellular cytotoxicity (ADCC) mediated by one or more of the Fcγ receptors on the surface of granulocytes, macrophages and NK cells.

	Important information about its composition: Rituximab is a genetically engineered chimeric mouse/human monoclonal antibody representing a glycosylated immunoglobulin with human immunoglobulin (Ig) G1 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.
Hyperlink to the Product Information	Link
Indication(s) in the EEA	Non-Hodgkin's lymphoma (NHL) Rituximab is indicated for the treatment of previously untreated adult patients with stage III-IV follicular lymphoma in combination with chemotherapy. Rituximab maintenance therapy is indicated for the treatment of adult follicular lymphoma patients responding to induction therapy. Rituximab monotherapy is indicated for treatment of adult patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy. Rituximab is indicated for the treatment of adult patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) chemotherapy. Rituximab in combination with chemotherapy is indicated for the treatment of paediatric patients (aged ≥ 6 months to < 18 years old) with previously untreated advanced stage CD20 positive diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL)/Burkitt leukaemia (mature B-cell acute leukaemia) (BAL) or Burkitt-like lymphoma (BLL). Chronic lymphocytic leukaemia (CLL) Rituximab in combination with chemotherapy is indicated for the treatment of patients with previously untreated and relapsed/refractory CLL. Only limited data is available on efficacy and safety for patients previously treated with

	monoclonal antibodies including Rituximab or patients refractory to previous rituximab plus chemotherapy. Rheumatoid arthritis (RA) Rituximab in combination with methotrexate is indicated for the treatment of adult patients with severe active RA who have had an inadequate response or intolerance to other disease-modifying anti-rheumatic drugs (DMARD) including one or more tumour necrosis factor (TNF) inhibitor therapies. Rituximab has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate. Granulomatosis with polyangiitis and microscopic polyangiitis Rituximab, in combination with glucocorticoids, is indicated for the treatment of adult patients with severe, active granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA). Rituximab, in combination with glucocorticoids, is indicated for the induction of remission in paediatric patients (aged ≥ 2 to < 18 years old) with severe, active GPA (Wegener's) and MPA. Pemphigus vulgaris Rituximab is indicated for the treatment of patients with moderate to severe PV.
	Proposed (if applicable): Not applicable.
Dosage in the EEA	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 (BSA) per cycle, for up to 8 cycles. Rituximab should be administered on day 1 of each chemotherapy cycle, after intravenous (IV) 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 BSA 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 BSA 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/m2 BSA, administered as an IV 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 BSA, administered as an IV infusion once weekly for four weeks. <u>Adult Diffuse large B cell non-Hodgkin's lymphoma</u> Rituximab should be used in combination with CHOP chemotherapy. The recommended dosage is 375 mg/m^2 BSA, administered on day 1 of each chemotherapy cycle for 8 cycles after IV 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. <u>Chronic lymphocytic leukaemia</u> The recommended dosage of rituximab in combination with chemotherapy for previously untreated and relapsed/refractory patients is 375 mg/m^2 BSA administered on day 0 of the first treatment cycle followed by 500 mg/m^2 BSA administered on day 1 of each subsequent cycle for 6 cycles in total. The chemotherapy should be given after rituximab infusion. <u>Rheumatoid arthritis</u>

	Patients treated with rituximab must be given the patient alert card with each infusion. A course of rituximab consists of two 1000 mg IV infusions. The recommended dosage of rituximab is 1000 mg by IV infusion followed by a second 1000 mg IV infusion two weeks later. The need for further courses should be evaluated 24 weeks following the previous course. Retreatment should be given at that time if residual disease activity remains, otherwise retreatment should be delayed until disease activity returns. <u>Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA)</u> Patients treated with rituximab must be given the patient alert card with each infusion *Adult induction of remission* The recommended dosage of rituximab for induction of remission therapy in adult patients with GPA and MPA is 375 mg/m2 BSA, administered as an IV infusion once weekly for 4 weeks (four infusions in total). *Adult maintenance treatment* Following induction of remission with rituximab, maintenance treatment in adult patients with GPA and MPA should be initiated no sooner than 16 weeks after the last rituximab infusion. Following induction of remission with other standard of care immunosuppressants, rituximab maintenance treatment should be initiated during the 4-week period that follows disease remission. Rituximab should be administered as two 500 mg IV infusions separated by two weeks, followed by a 500 mg IV infusion every 6 months thereafter. Patients should receive rituximab for at least 24 months after achievement of remission (absence of clinical signs and symptoms). For patients who may be at higher risk for relapse, physicians should consider a longer duration of rituximab maintenance therapy, up to 5 years. <u>Pemphigus vulgaris</u> Patients treated with rituximab must be given the patient alert card with each infusion. The recommended dosage of rituximab for the treatment of PV is 1000 mg administered as an IV infusion followed two weeks

	later by a second 1000 mg IV infusion in combination with a tapering course of glucocorticoids. *Maintenance treatment* A maintenance infusion of 500 mg IV should be administered at months 12 and 18, and then every 6 months thereafter if needed, based on clinical evaluation. *Treatment of relapse* In the event of relapse, patients may receive 1000 mg rituximab IV. The healthcare provider should also consider resuming or increasing the patient's glucocorticoid dose based on clinical evaluation. Subsequent infusions may be administered no sooner than 16 weeks following the previous infusion.
	Proposed (if applicable): Not applicable.
Pharmaceutical form(s) and strengths	Current (if applicable): • Rituximab 100 mg concentrate for solution for infusion • Rituximab 500 mg concentrate for solution for infusion
	Proposed (if applicable):
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Not applicable for biosimilar application.

Part II: Module SII - Non-clinical part of the safety specification

1.1 Toxicity

1.1.1 Single- and repeat-dose toxicity studies with reference product MabThera

In single- and repeat-dose IV toxicity studies, rituximab was non-toxic to monkeys at the various doses and schedules studied.

In the GLP single dose toxicology study, rituximab was administered intravenously at a dose of 10-, 30-, or 100 mg/kg to one male and one female per dose group. There were no treatment-related effects on mortality, body weight, food consumption or body temperature. There was a transient and mild decrease in platelet count, a decrease in lymphocyte ratio, and an increase in neutrophil ratio for both sexes in the 30 and 100 mg/kg dose groups. All hematologic changes were mild, dose independent and returned to baseline by Day 7 or 14; therefore, they were not considered to be biologically significant. In the repeat-dose GLP toxicology study, animals were administered rituximab intravenously at doses of 0 or 20 mg/kg weekly for 4 or 8 weeks.

Animals were euthanized 2 weeks after their last dose. There were no treatment-related effects on mortality, body weight, food consumption, hematology parameters, clinical chemistry, or urinalysis parameters. A possible treatment-related clinical observation included vomiting approximately 15-20 minutes after drug administration in three of the treated female animals (once in 1 female treated for 4 weeks; occasionally in 2 females treated for 8 weeks). The toxicological significance of these events is difficult to interpret given the low incidence and the absence of similar events in treated males. All other effects were consistent with the expected pharmacologic activity of rituximab; decreased B cells by flow cytometry in peripheral blood, lymph nodes, and femoral bone marrow; small spleens in four of the treated animals; histopathologic lymphoid atrophy in the spleen, mandibular lymph nodes, and submucosal lymphoid nodules of the colon; and decreased B cells by immunohistochemistry in the mandibular lymph nodes and spleen.
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Relevance to human usage: Yes

Discussion:

Decline of peripheral B-cell counts in human beings, associated with its pharmacological action.

1.1.2 Toxicology studies

The in vivo toxicology program conducted in cynomolgus monkeys identified pharmacological effects that are consistent with the anticipated findings for a B cell depleting therapy and included decreased peripheral B-cells, decreased B-cells in tissues, lymphoid atrophy, and alterations in haematology related to decreased B-cells.

Relevance to human usage: Yes

Discussion:

Potential increased susceptibility to infection or an inadequate response to vaccination due to B-cell immunocompromisation.

1.1.3 Reproductive toxicity

Rituximab was administered weekly to pregnant female monkeys during the period of organogenesis at doses of 20, 50, or 100 mg/kg. There were no findings of toxicity to the dams or developing foetuses. The only effect noted was the dose-dependent pharmacologic depletion of B cells in the lymphoid organs of the foetuses. B-cell depletion following exposure in utero, which appeared to be reversible in infants once drug had cleared or fallen to non-effective levels.

Relevance to human usage: Yes

Discussion:

No toxicity expected apart from B-cell depletion. Potential risk is that maternal exposure to rituximab may lead to B-cell depletion in the human foetus/infant, either from in utero exposure, or from exposure to rituximab in breast milk in nursing infants.

1.1.4 Embryofetal toxicity

Potential risk of embryofetal toxicity resulting from systemic exposure to Recombinant Human PH20 (hyaluronidase)(rHuPH20) (rituximab subcutaneous [SC]).

Relevance to human usage: No

Discussion:

Potential risk of embryofetal toxicity based on a very conservative interpretation of pharmacokinetic (PK) and toxicology data in animal studies at very high systemicexposure levels (reductions in fetal weight and increased number of resorptions) but did not show overt dysmorphogenic (i.e., teratogenic) potential. These findings are consistent with current knowledge of the natural activity of hyaluronidase. Studies in knock-out mice have demonstrated the importance of hyaluronan in normal heart development. No data in humans have been collected and potential seriousness and outcomes are unforeseeable at this point in time.

1.2 General Safety Pharmacology

1.2.1 Mechanisms for drug interactions

The elimination of rituximab is mediated by both the specific CD20 receptor-mediated pathway and the non-specific IgG clearance pathways. These data suggest that rituximab would not be expected to have many of the common mechanisms of drug-drug interactions with small molecules, including changes in protein binding, P450 activity, and transporters.

Relevance to human usage: No

Discussion:

Although no specific drug interaction studies have been performed, based on pharmacokinetic (PK) data from Phase II/III studies, cyclophosphamide (CYC), methotrexate (MTX), and corticosteroids seemed to have little or no effect on the pharmacokinetics of rituximab.

Part II: Module SIII - Clinical trial exposure

The clinical trial exposure with reference medicinal product MabThera® is presented in

Table 1.

Table 1 Clinical Trial Exposure with MabThera®

Indication	Number of patients exposed to Rituximab in Company Pivotal Trials
Rheumatoid Arthritis	3,595[1]
Granulomatosis with Polyangiitis and Microscopic Polyangiitis	181[2]
Non-Hodgkin's Lymphoma (intravenous and subcutaneous)	3,474[3]
Chronic Lymphocytic Leukaemia (intravenous and subcutaneous)	914[4]
Pemphigus vulgaris	38[5]

[1]Data cut-off: September 2012.

[2]Total Number includes RAVE, ML22514 and WA25615 study.

[3]Total Number includes studies BP22333, B022334, MO18264, U4391G, MO28107 and MO28457 and BO25380 data cut off dates vary and details are provided under respective sections below.

[4]Total Number includes studies B017072, ML17102, B025341, data cut off dates vary and details are provided under respective sections below.

[5]In study ML22196, patient disposition in Rituximab + Prednisone arm: N=46 - PV=38, pemphigus foliaceus (PF)=8.

The following studies are being conducted with Ituxredi, also referred to as DRL_RI in this document, which is being developed for IV administration as a similar biological medicinal product for the indications approved for the reference product MabThera®. The objective of the clinical development programme is to generate data confirming biosimilarity of DRL_RI with the United States (US) reference product Rituxan®, which was licensed in the US in November 1997 and the European Union (EU) reference medicinal product MabThera®, which was approved in the EU in June 1998.

The favourable risk-benefit profile of MabThera® in the approved indications has been well-documented; therefore, it is expected that a robust demonstration of similarity between DRL_RI and MabThera® will support the conclusion that the risk-benefit ratio of DRL_RI in these indications will be equally favourable.

The clinical biosimilarity assessment for DRL_RI is supported by chemistry, manufacturing and controls (CMC) analytical studies, binding and cell-based assays, and non-clinical studies.

Furthermore, three clinical studies are included in the clinical biosimilarity assessment of DRL_RI compared with MabThera® and Rituxan®:

- RI-01-003: 3-way PK equivalence study in Rheumatoid Arthritis patients

- RI-01-006: Comparative efficacy study in Low Tumour Burden Follicular Lymphoma (LTB-FL) patients
- RI-01-007: Switch study in Rheumatoid Arthritis patients

DRL has completed a Phase I clinical trial (RI-01-003 study), to compare PK/PD response to treatment with DRL_RI, Rituxan® and MabThera® in patients with RA. The RI-01-003 study demonstrated comparable PK and safety between DRL_RI, Rituxan® and MabThera®. DRL has conducted an Efficacy, Safety and Immunogenicity study in LTBFL patients (RI-01-006) and Transition Study in RA patients (RI-01-007). The clinical studies, RI-01-003, RI-01-006 and RI-01-007 are summarised in **Error! Reference source not found.**.

Table 3 Overview of Clinical Development Plan for DRL_RIStudy No.	Study Title	Study Type	Patient Population	Study Treatments	Countries	Objectives

RI-01-003	A Double-blind, Randomized, Parallel Group Study Comparing the Pharmacokinetics, Pharmacodynamics, Safety, Efficacy, and Immunogenicity of Three Anti-CD20 Monoclonal Antibodies in Patients with Moderate to Severe Active, Seropositive Rheumatoid Arthritis with an Inadequate Response to Methotrexate Based Therapy	PK/PD	Rheumatoid arthritis (RA) N = 276	DRL_RI Rituxan® MabThera®	India Ukraine	Primary: • Comparison of PK profiles of DRL_RI, U.S. RP (Rituxan®) and European Reference Medicinal Product (MabThera®) Secondary: • Comparison of magnitude and kinetics of response to therapy based on change in disease activity score (DAS28-CRP) at 4-week intervals • Comparison of extent and kinetics of B cell depletion • Comparison of efficacy, safety (including B cell recovery) and tolerability • Comparison of immunogenicity
RI-01-006	A Randomized, Double-blind, Parallel-group, Phase III Study to Compare the	Efficacy, Safety, and Immunogenicity	LTBFL N = 312	DRL_RI MabThera®	Belarus Bosnia and Herzegovina Bulgaria	<u>Primary:</u> • To demonstrate the equivalent efficacy of DRL_RI and MabThera® in subjects with B-lymphocyte

	Efficacy, Safety, and Immunogenicity of Proposed Rituximab Biosimilar (DRL_RI) with MabThera® in Subjects with Previously Untreated, Stage II-IV, Cluster of Differentiation (CD)20-Positive, Low Tumour Burden Follicular Lymphoma				Czech Republic Georgia Greece India Italy South Korea Poland Romania Russian Federation Serbia Spain Turkey Ukraine USA	antigen CD20-positive, LTBFL, as measured by ORR at Week 28, evaluated in accordance with published response criteria for malignant lymphoma. Secondary: • To compare the PFS, ORR at Week 12, OS, and DOR of DRL_RI with MabThera® in subjects with CD20-positive, LTBFL. • To compare the safety, tolerability, and immunogenicity of DRL_RI with MabThera® in subjects with CD20-positive, LTBFL. Exploratory • To compare ORR evaluated in accordance with the Lugano criteria (Cheson et al,1999) in subjects with CD20-positive, LTBFL treated with either DRL_RI or MabThera®.

Table 3 Overview of Clinical Development Plan for DRL_RIStudy No.	Study Title	Study Type	Patient Population	Study Treatments	Countries	Objectives
						• To explore the PK parameters of DRL_RI and MabThera®, using a population-PK modelling approach. • To explore the pharmacodynamic parameters of DRL_RI and MabThera®.

Table 3 Overview of Clinical Development Plan for DRL_RIStudy No.	Study Title	Study Type	Patient Population	Study Treatments	Countries	Objectives
RI-01-007	A randomized, double-blind, parallel group, multicentre study to assess the immunogenicity and safety of transitioning subjects with rheumatoid arthritis to biosimilar rituximab (DRL_RI) or continued treatment with Rituxan® or MabThera®	Safety and Immunogenicity upon Single Transition	RA N = 140 (70 per treatment arm)	DRL_RI Rituxan® MabThera®	Bulgaria Czech Republic Germany Hungary Lithuania Poland United States of America	• To compare the immunogenicity of transitioning subjects with RA to DRL_RI from Rituxan (US-rituximab)/MabThera (EU-rituximab) to continued treatment with Rituxan® or MabThera®. • To compare the safety of transitioning subjects with RA to DRL_RI from Rituxan® or MabThera® to continued treatment with Rituxan® or MabThera®.

DOR: duration of response, DRL_RI: Dr. Reddy's Laboratories Rituximab biosimilar, EU: European Union LTBFL: Low Tumour Burden Follicular Lymphoma, OS: overall survival, RA: rheumatoid arthritis, USA: United States of America.

Study RI-01-003

A randomized, double blinded, comparative clinical study to compare efficacy, safety, and immunogenicity of DRL_RI, Rituxan, and MabThera in adult patients aged 18 to 65 years with moderate to severe active, seropositive RA with an inadequate response to methotrexate (MTX)-based therapy. Patients enrolled were receiving MTX weekly therapy for at least 6 months and had active RA (according to the 1987 American College of Rheumatology [ACR] criteria) of at least 6 months duration with > 6 tender joints and a > 6 swollen joint count (from the 66/68 joint count system); at least a moderate disease activity defined as: serum C-reactive protein (CRP) level 2 ≥ 1 x upper limit of normal (ULN) or erythrocyte sedimentation rate ≥ 28 mm; positive rheumatoid factor (RF) or anti-cyclic citrullinated peptide antibodies; DAS28-CRP > 3.2 despite stabilized therapy (at least last 3 months for MTX and 4 weeks for additional non-MTX DMARDs with 1 or 2 non-biological DMARDs including MTX monotherapy 15 to 25 mg per week or MTX 10 to 25 mg per week in combination with other non-biological DMARD for at least 6 months.

A total of 276 patients (DRL_RI: N = 92, Rituxan: N = 92, MabThera: N = 92) were planned to be randomized to ensure 246 evaluable patients (82 per treatment arm). Randomization was stratified by gender. Given that the study was also conducted at study sites in Ukraine, “regions” was applied as a stratification factor for randomization.

This study was conducted across 29 sites (22 sites in India and 7 sites in Ukraine). The primary objective of the study was to compare the plasma PK profile of DRL_RI (proposed biosimilar for rituximab by Dr. Reddy’s Laboratories [DRL]), Rituxan®, and MabThera® in patients with RA over one course of therapy, consisting of two doses to be administered 2 weeks apart.

Study RI-01-006

Study 006 was a randomized, double-blind, parallel-group, equivalence, multicentre Phase 3 study to compare the efficacy, safety, and immunogenicity of DRL_RI with MabThera in patients with previously untreated, Stage II-IV, CD20-positive LTBFL.

A total of 317 patients were randomized from 142 study sites worldwide and received either DRL_RI or MabThera. The study plan was as follows: induction treatment consisting of a weekly IV infusion for 4 weeks (375 mg/m^2 of BSA) followed by maintenance treatment consisting of an IV infusion (375 mg/m^2 of BSA) every 8 weeks starting at Week 12 until Week 36. After completion of the maintenance treatment period, patients were planned to be followed up until 52 weeks after the first dose of study drug (at Weeks 44 and 52). The data of patients up to Week 28 is presented in the submitted report and the dossier.

The primary objective of this study was to demonstrate the equivalent efficacy of DRL_RI and MabThera® in subjects with B-lymphocyte antigen CD20-positive, LTB-FL, as measured by ORR up to Week 28, evaluated in accordance with published response criteria for malignant lymphoma (Cheson et al, 1999).

Study RI-01-007

Study 007 was a randomized, double-blind, parallel group, multicentre Phase 3 transition study to assess the immunogenicity and safety of transitioning subjects with RA to DRL_RI or continued treatment with Rituxan or MabThera. The evaluation of safety and immunogenicity upon transition

from a registered medicinal product to a biosimilar product is a requirement of US Food and Drug Administration.

Approximately 140 patients with RA who have received at least one full course of treatment comprising two 1000 mg infusions with either Rituxan or MabThera were planned to be randomized to receive either two 1000 mg infusions of DRL_RI (in combination with MTX) or Rituxan/MabThera on Day 1 and Day 15. After completing the treatment period, patients were followed-up for 24 weeks. The study consisted of a screening period (Days -14 to Day 0) and a double-blind period (Day 1 to Week 12). Participants attended a screening visit followed by visits at Weeks 0 (Day 1), 2, 4, 8, and 12 (end of study) after randomization.

The primary objective of the study was to assess the immunogenicity of transitioning subjects with RA to DRL_RI (biosimilar rituximab) from US-rituximab/EU-rituximab to continued treatment with US-rituximab/EU-rituximab.

Other Supportive Studies

Study RI-01-002, a randomized, multicentre, double-blind, parallel group study, was conducted in previously untreated adult patients with CD20-positive DLBCL to compare the PK, PD, safety, efficacy, and immunogenicity of two anti-CD20 monoclonal antibodies (DRL-rituximab [RedituxTM] and reference medicinal product MabThera) in combination with CHOP in India. A total of 151 patients were enrolled in the study.

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Table 2 Important Exclusion Criteria in the Pivotal Clinical Studies for MabThera®

Criterion	Reason for Exclusion	Is It to be Included as Missing Information (Yes/No)?	If No, Rationale
Hypersensitivity	Hypersensitivity is a rare occurrence. Patients with hypersensitivity to rituximab are not treated.	No	As per the EU SmPC, MabThera is contraindicated in patients with hypersensitivity to the active substance or to murine proteins, or to any of the excipients.
Active, severe infections	Serious infections, including fatalities, can occur during therapy with rituximab. Rituximab should not be administered to patients with an active, severe infection (e.g., tuberculosis, sepsis and opportunistic infections). Physicians should exercise 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 (e.g., hypogammaglobulinaemia).	No	As per the EU SmPC, MabThera is contraindicated in patients with active, severe infections.

Criterion	Reason for Exclusion	Is It to be Included as Missing Information (Yes/No)?	If No, Rationale
Patients in a severely immunocompromised state	Serious infections, including fatalities, can occur during therapy with rituximab. Rituximab should not be administered to severely immunocompromised patients (e.g., where levels of CD4 or CD8 are very low). Physicians should exercise 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 (e.g., hypogammaglobulinemia). It is recommended that immunoglobulin levels are determined prior to initiating treatment with rituximab.	No	As per the EU SmPC, MabThera is contraindicated in patients in a severely immunocompromised state.
Severe heart failure (New York Heart Association Class IV) or severe, uncontrolled cardiac disease*	Angina pectoris, or cardiac arrhythmias such as atrial flutter and fibrillation, heart failure and/or myocardial infarction have occurred in patients treated with MabThera. Therefore, patients with a history of cardiac disease and/or cardiotoxic chemotherapy should be monitored closely.	No	As per the EU SmPC, MabThera is contraindicated (in non-oncology indications) in patients with severe heart failure (New York Heart Association Class IV) or severe, uncontrolled cardiac disease.

Fertile men or women of childbearing potential not using adequate contraception (oral contraceptives, intrauterine device or barrier method of contraception in conjunction with spermicidal jelly or surgically sterile). Pregnant or breastfeeding women.	Due to the long retention time of rituximab in B cell depleted patients, women of childbearing potential should use effective contraceptive methods during and for 12 months following treatment with MabThera. Pregnancy: IgG immunoglobulins are known to cross the placental barrier. There are no adequate and well- controlled data from studies in pregnant women; however transient B-cell depletion and lymphocytopenia have been reported in some infants born to mothers exposed to MabThera during pregnancy. For these reasons MabThera should not be administered to pregnant women unless the possible benefit outweighs the potential risk. Breast-feeding: Limited data on rituximab excretion into breast milk suggest very low milk levels (relative infant dose less than 0.4%). Few cases of follow-up of breastfed infants describe normal growth and development up to 1.5 years. However, as these data are limited and the long-term outcomes of breastfed infants remain unknown, breastfeeding is not recommended while being treated with rituximab and optimally for 12 months following rituximab treatment.	No	'Use in pregnancy and lactation (all indications)' is no longer presented as missing information and does not require active risk management in line with GVP Module V (Rev 2). Use in pregnancy and lactation will continue to be presented and evaluated in the PSUR as part of routine pharmacovigilance activities.
Administration of live vaccines to be completed	In a non-randomized study, patients with relapsed low-grade non-Hodgkin's lymphoma (NHL) who	No	As per the EU SmPC Special warnings and precautions for

Criterion	Reason for Exclusion	Is It to be Included as Missing Information (Yes/No)?	If No, Rationale
at least 4 weeks prior to commencing treatment	received rituximab monotherapy when compared to healthy untreated controls had a lower rate of response to vaccination with tetanus recall antigen (16% vs. 81%) and Keyhole Limpet Haemocyanin (KLH) neoantigen (4% vs. 69% when assessed for >2-fold increase in antibody titre). For chronic lymphocytic Leukaemia (CLL) patients, similar results are assumable considering similarities between both diseases but that has not been investigated in clinical trials.		use, the safety of immunization with live viral vaccines, following MabThera therapy has not been studied. Vaccination with live virus vaccines is not recommended whilst on MabThera or whilst peripherally B cell depleted. Patients treated with MabThera may receive non-live vaccinations. However, response rates to non-live vaccines may be reduced.
Patients under 18 years of age (except of (paediatric) PePRS study WA25615 and Intergroup B-NHL-2010 trial.	The safety and efficacy of rituximab in children below 18 years has not been established in indications other than GPA and MPA (for patients ≥ 2 to < 18 years of age), and B-NHL (aged ≥ 6 months to < 18 years old).	No	As per the EU SmPC, Section 4.2 Posology and method of administration, safety and efficacy of MabThera in paediatric patients (≥ 2 to < 18 years of age) has not been established in diseases other than GPA or MPA or B-NHL (aged ≥ 6 months to < 18 years old).

CHMP: Committee for Medicinal Products for Human Use; CLL: Chronic Lymphocytic Leukaemia; EU: European Union; GPA: Granulomatosis with Polyangiitis, MPA: Microscopic Polyangiitis; NHL: Non-Hodgkin's lymphoma; SmPC: Summary of Product Characteristics.

* It is applicable only for non-oncology indication(s)

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Use in Pregnancy and Lactation

The safety of using rituximab while pregnant or breastfeeding is not fully known, as pregnant and lactating women are excluded from clinical trials. Additionally, all patients in clinical trials (male and female) are required to use effective contraception during trial participation, and females of childbearing potential must have a negative urine pregnancy test within two weeks prior to randomization or rescue therapy.

Rituximab should not be administered to pregnant women unless the possible benefit outweighs the potential risk and due to the long retention time of rituximab in B-cell depleted patients, women of childbearing age must employ effective contraceptive methods during and for 12 months after treatment with rituximab. Moreover, breastfeeding is not recommended while being treated with rituximab and optimally for 6 months following rituximab treatment.

Table 3 Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development program.
Breastfeeding women	Not included in the clinical development program.
Patients with Relevant Comorbidities	
Patients with renal impairment (with significantly elevated serum creatinine [e.g., > 1.5 x ULN or > 2.5 x ULN] or creatinine clearance [< 60 - 70 ml/min])	Not included in the clinical development program. *Note*: the restriction related specifically to the concomitant (potentially nephrotoxic) chemotherapy given for malignant haematological disorders, since rituximab is not renally excreted and is not nephrotoxic.
Patients with hepatic impairment (with poor hepatic function [e.g., bilirubin > 2 x ULN and/or alkaline phosphatase and/or transaminases > 2 x ULN])	Not included in the clinical development program. *Note*: the restriction is mainly due to the concomitant chemotherapy (notably cyclophosphamide) given for malignant haematological disorders, since rituximab does not undergo hepatobiliary excretion and is not hepatotoxic.
Patients with cardiac impairment (with poor function/severe impairment [variously defined])	Not included in the clinical development program. *Note*: restriction is *partly* due to the concomitant chemotherapy given to for malignant hematological disorders, some of which are known to be cardiotoxic (notably anthracyclines).
Population with relevant different ethnic origin	Not included in the clinical development program.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program.
Other:	
Children	Not included in the clinical development program.

Part II: Module SV - Post-authorisation experience

SV.1 Post-Authorisation Exposure

SV.1.1 Method Used to Calculate Exposure

Estimation of non-study post-authorisation exposure data is based on the worldwide sales data of DRL's rituximab. Further elaborated sales data that could facilitate the calculation of person time or stratification by age, gender or indication is not available. Therefore, the sales data available as number of packs sold per strength since the launch of DRL's rituximab in countries worldwide has been summarised below.

The cumulative patient exposure estimates cover the period from international birth date (IBD) until November 202.

SV.1.2 Exposure

Table 4 Number of DRL's Rituximab units/vials Soldand by Country Since the Launch of the Product

Country	Total volume of units/vials sold
Algeria	17,800
Azerbaijan[#]	3,650
Belarus[#]	5,500
Chile[#]	4,968
Ecuador[#]	1,080
Guatemala	4,865
Honduras[#]	14,730
India	765,152
Indonesia	35,050
Jamaica	3,074
Kyrgyzstan[#]	21
Maldives	1,400
Mauritius	620
Myanmar	4,995
Nepal	7,880
Peru[#]	15,755
Philippines	9,400
Russia	1,094,196

Country	Total volume of units/vials sold
South Africa	11,381
Sri Lanka	26,941
Thailand	103,914
Trinidad & Tobago	7,715
Tunisia	20,758
Turkey	283,229
Ukraine	80,311
Vietnam	118,531
Grand Total	**2,642,916**

The total worldwide exposure to DRL's rituximab since first market launch as of 17 November 2024 is estimated to be 2,642,916 standard units of various strengths.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Drugs that have potential for misuse for illegal purposes are expected to share some general characteristics, such as psychoactive effects or, less commonly, anabolic effects or enhancement of haemoglobin levels. The lack of evidence of such side-effects that may lead to misuse for illegal purposes, in addition to the Warnings and Precautions section of the SmPC (which states that rituximab should be administered in an environment where full resuscitation facilities are immediately available, and under the close supervision of an experienced physician) make it highly unlikely that there is a potential for misuse of rituximab for illegal purposes. To date, no reports of misuse of rituximab for illegal purposes have been received.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of Safety Concerns in the Initial Risk Management Plan (RMP) Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.2 New Safety Concerns and Reclassification With a Submission of an Updated RMP

The safety concerns “Hepatitis B reactivation (All indications)” and “Hypogammaglobulinaemia (Non-oncology indications)” which were previously classified as important identified risks are no longer presented inline with the reference medical product RMP as there are no additional activities/measures needed to further characterize these risks.

The use of rituximab has been associated with hepatitis B reactivation in Hepatitis B Surface Antigen (HBsAg)+ve as well as HBsAg-ve/Hepatitis B Core Antibody (HBcAb)+ve patients, particularly when administered in combination with immunosuppressive therapies such as steroids or chemotherapy, across all indications. and the current EU SmPC provides a comprehensive description of this event, including clinical symptoms, potential mechanisms, diagnosis, risk factors, and preventability. the MAH recommends hepatitis B Virus (HBV) screening in all patients before the initiation of treatment with rituximab in all indications, and that patients with positive serology should consult with a liver disease specialist before start of treatment. Those patients should be monitored and managed following local standards to prevent hepatitis B reactivation.

Rituximab acts via binding to transmembrane antigen CD20, which is located on pre-Band mature B-lymphocytes. Although antibody-producing plasma cells are not directly affected by rituximab, patients can develop prolonged B-cell depletion resulting in antibody deficiency. Hypogammaglobulinemia itself is asymptomatic but may predispose the patient to certain infections. The current EU SmPC contains Routine risk minimization activities recommending specific clinical measures to address the risk: Immunoglobulin levels are recommended to be determined prior to initiating treatment with Ituxredi. Hypogammaglobulinemia can be treated with IV immunoglobulins. Healthcare professionals are informed via EU SmPC and aware of the risks of hepatitis B reactivation and hypogammaglobulinemia and have the appropriate measures in place as part of clinical practice.

The MAH continues routine PV activities including signal detection.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

1.1 INFECTIONS, INCLUDING SERIOUS INFECTIONS (ALL INDICATIONS)

Potential mechanisms:

All Indications

Rituximab's anticipated mechanism of action induces B-cell depletion that can lead to a depressed immune system. In addition, previous or concomitant immunotherapy, bone marrow infiltration, and/or corticosteroid therapy can be important contributing factors.

For NHL/CLL; underlying disease can also contribute to immunosuppression. It is possible that B-cell depletion ± associated hypogammaglobulinaemia caused by rituximab could increase the risk of severe viral infections or viral reactivation and opportunistic infections, especially in patients with other predisposing conditions (e.g., T-cell deficiencies, bone marrow infiltration and/or immunotherapy, concomitant chemotherapy, previous immunosuppressive therapy).

The following details are from the reference medicinal product (MabThera).

Evidence source(s) of linking the risk to the medicine and strength of evidence (from reference medicinal product MabThera data):

- MabThera® SmPC
- Drug Safety Report (DSR) No 1066792 on Infections (dated March 2016)
- DSR 1027733 on infections (dated 29 October 2007), and references therein.
- DSR 1022732 on viral infections (dated August 2006) and references therein.
- DSR 1027731 (dated 29 October 2007), 1044830 (dated 30 June 2011).
- 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 (cut-off: 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).
- DSR 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.
- RaVeR (WA27893) 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 (cut-off: July 2012) comprising M39021, M39022, M39045, E4494. E1496, PRIMA (MO18264), CLL8/ML17102, and BO17072/REACH
- Clinical Study Reports for Study ML17102/CLL 8 and BO17072/REACH and PRIMA (MO18264) studies.
- CSR 1088458 study Inter B NHL Ritux 2010 (11 March 2019)

Characterization of the risk:

Frequency with 95% Confidence Interval (CI):

RA

The overall rate of infection was 75.7 events per 100 patient years. This was numerically less than that observed in the pooled placebo population (90.39 events per 100 patient years) and was stable across multiple treatment courses (MabThera).

The overall rate of serious infection in rituximab-treated patients was 3.76/100 patient- years (2.71/100 patient-years in patients observed for > 5 years). This is comparable with placebo populations (3.79; CI: 2.80; 5.13) and the rate remained stable over time and across multiple treatment courses (DSR 1066792, dated March 2016).

Bacterial infections were seen in 9% of patients, the biggest share of those being bacterial cellulitis at 3%. Species specific reporting was led by Staphylococci and Streptococci though both accounted for < 1% each (DSR 1066792, dated March 2016).

Viral infections had the highest proportion of pathogen specific infections reported, at 19%. Influenza viruses accounted for 8% of those, followed by Herpesviridae family at 7% and viral gastroenteritis at 3%.

Fungal infections were reported in 9% of events; vulvovaginal mycotic infection and tinea pedis accounted for 3% each (DSR 1066792, dated March 2016).

In the All Exposure RA population, 22 potential opportunistic infections (of 12 different types) were identified in 21 (5.8%) patients (rituximab 0.05 events/100 patient-years; placebo, 0.09 events/100 patient-years).

GPA/MPA

In RAVE, the rate of serious infections (per patient-year) was similar between the two treatment groups (0.25 for rituximab, 0.28 for cyclophosphamide) at 6 months. The proportions of patients who experienced serious infections by 18 months were also similar between the rituximab (15 patients or 15.2%) and cyclophosphamide (15 patients or 15.3%) groups. The rates of serious infections (per patient-year) were also similar between the two groups at 18 months: 0.13 with 95% CI: 0.08; 0.20 for the rituximab group and 0.16 with 95% CI: 0.10; 0.24 for the cyclophosphamide group (MabThera).

The frequency of serious adverse events (SAEs) was similar to that seen in other studies of vasculitis patients and appeared to largely reflect the influence of concurrent or previous immunosuppressive therapy, underlying disease, and corticosteroid therapy.

As *Pneumocystis* infections are known to occur in GPA/MPA, patients in RAVE were required to receive *Pneumocystis* prophylaxis. After the 6-month remission induction phase and the 12-month remission maintenance phase period of the RAVE study, there had been a total of 2 non-serious opportunistic infections (*Mycobacterium avium* complex and oesophageal *Candida*) reported in the rituximab group, and 2 opportunistic infections (1 serious and 1 non-serious) in the cyclophosphamide treatment group (MabThera).

In Study WA27893 (RaVeR) in adults, fourteen patients had 24 serious infections, for an incidence rate of 7.11 per 100 patient years. The infection profile observed in this study was consistent with the known safety profile of rituximab in the patient population.

In Study ML22514 in adults, infections occurred at a comparable frequency between the arms (53% rituximab vs. 57% azathioprine). The incidence of serious infections was similar (12%) in both arms. The infection profile observed in this study was consistent with the known safety profile of rituximab in the patient population. Three patients reported opportunistic infections; two patients in the rituximab arm experienced one event each of severe oesophageal candidiasis and moderate *Pneumocystis jirovecii* pneumonia, and one patient in the azathioprine arm experienced moderate atypical mycobacterial pneumonia. No events of progressive multifocal leukoencephalopathy (PML), or hepatitis B reactivation were reported in this study.

In the DSR 1081144, a total of 126 adverse events (AEs) (19.8%) including 102 SAEs were reported in the MedDRA System Organ Class (SOC) Infections and infestations. The most frequently reported PTs in this SOC were infection, pneumonia, lower respiratory tract infection, sinusitis and pneumonia bacterial; the reported infections are consistent with the known safety profile of rituximab. No event of PML was reported in the DSR 108114.

In paediatric study WA25615 (PePRS), during the overall study period, 105 infection AEs were reported in 23 patients (92%), of which the majority (96 out of 105 AEs [91%]) were reported to be non-serious. Similar to the Remission Induction Phase, the most frequently reported infections during the overall study period were upper respiratory tract infections (12 patients [48%]), all of which were non-serious.

Pemphigus vulgaris

In Study ML22196, fourteen patients (36.8%) in the rituximab + prednisone arm experienced 43 treatment-related infections and 15 patients (41.7%) in the prednisone alone arm experienced 28 treatment-related infections. The most frequent infection preferred terms (PTs) (occurring in 5% in either treatment arm [rituximab + prednisone arm vs. prednisone), were: bronchitis (3 patients [7.9%] vs. 7 patients [19.4%1]), urinary tract infection (2 patients [5.3%] vs. 3 patients [8.3%1]), fungal infection (2 patients [5.3%] vs. 2 patients [5.6%1]), skin bacterial infection (1 patient [2.6%] vs. 3 patients [8.3%1]), herpes virus infection (3 patients [7.9%] vs. 0 patients), herpes zoster (2 patients [5.3%] vs. 1 patient [2.8%]), oral herpes (2 patients [5.3%] vs. 1 patient [2.8%]), and conjunctivitis (2 patients [5.3%] vs. 0 patients).

In Study WA29330 (PEMPHIX), no opportunistic infections occurred during the study.

NHL/CLL

Infections are very common in patients receiving rituximab (10% of patients), based on pooled clinical trial experience.

In order to provide a coherent view of the rates of infections associated with use of rituximab in various patient sub-populations, the clinical data below are presented sub- divided by oncological indication and stage(s) when rituximab was administered (DSR 1066792, dated March 2016).

NHL Induction Only (8016368, M39021, M39045)

Forty-nine (49) % of patients (384 out of a total 778 patients) who received rituximab in the induction phase reported at least one infectious AE. In 47% of reported infectious events, the infectious agent was unspecified.

Bacterial infections were reported in 4.5% of patients. *E. coli* was the commonest bacterial pathogen (10 events), followed by *Staphylococcus* (7 events). No single type of infection, however, stood out and none accounted for more than 1% of events. The pattern was similar for serious infections with *E. coli* and Staphylococci leading the counts but no single event accounting for a majority share of events (MabThera).

Viral infections were reported in 5.4% patients, with Herpesviridae accounting for 2.7% and hepatitis B accounting for 0.3%. A similar trend was noted for serious infections (MabThera).

Fungal infections accounted for 2.3% patients with *Candida spp.* accounting for 1% of these, followed by *Pneumocystis* at 0.7%. A similar trend was observed for serious fungal infections with *Candida* causing 2 out of the 3 reported fungal SAEs(MabThera).

Opportunistic infections were reported in 0.6% cases (2 cases of Candida infection, 2 of Herpesviridae and 1 case of aspergillosis). No opportunistic bacterial infection was reported (DSR 1066792, dated March 2016).

NHL Induction and Maintenance (E1496, E 4494, M39022)

Sixty (60) % of patients in studies where rituximab was given during both induction and maintenance phases for NHL reported at least one infectious event, 7.7% of which were reported as serious; in 56% of cases the causative agents were unspecified.

Bacterial infections were reported in 3.2% of patients, but no single species was responsible for a majority of infections. In 1.2% patients, the bacterial infections were reported as serious, with *Clostridium difficile* reported in 0.2%.

Viral infections were reported in 5.7% of patients with Herpesviridae forming the largest group, being reported in 4.4% of patients. The majority of viral infections were non-serious, in only 1.1% of the patients being reported as serious; Herpesviridae remained the most common reported agent in this group.

Fungal infections were reported in 2.8% of patients, serious fungal infections reported in 1.8%. *Candida* was the most common reported fungal infectious agent at 1.8% of all infections and 0.6% of serious infections.

Opportunistic infections were reported in only 0.33% of patients, including one case of PJP. No viral or bacterial opportunistic infections were reported (DSR 1066792, dated March 2016).

NHL Maintenance Only (MO18264)

Forty-four (44) % of patients who received rituximab for maintenance therapy reported at least one infectious AE.

Bacterial infections accounted for 4.4% patients with *E. coli* reported most commonly at 1% and Staphylococci at 0.8%. Two cases of serious infections were reported.

Viral infections accounted for 7.2% patients, with *Herpes spp.* being the most significant recognized infectious agent in this group at 4.6%. Six cases of serious viral infections were noted, including one case of PML.

Fungal infections were reported in 1.8% of patients, with *Candida spp.* accounting for 0.8% of these cases. No serious fungal infections were reported.

Opportunistic infections were reported in only 2 cases which included one case of PML and one of mycobacterial infection. No fungal or bacterial opportunistic infections were reported (DSR 1066792, dated March 2016).

B-NHL paediatric (BO25380)

Infections were common during the overall treatment period of the study, occurring in 52.3% of subjects in the chemotherapy arm and 62.3% of subjects in the chemotherapy plus rituximab arm. The most common infections (10%) reported in the chemotherapy plus rituximab arm were sepsis (17.9%), device related infection (13.0%), and lung infection (13.0%).

CLL (BO17072, ML17102)

Thirty-three percent of patients administered rituximab in clinical trials reported at least one infectious adverse event; 18% of these were serious events. In 24% of these cases, the causative agent was unspecified.

Bacterial infections were reported in 2.1% of patients. Cellulitis was reported most commonly (0.3%) but no specific organism was noted. For serious infections, bacteria were reported in 1.8% patients.

A total of 9.6% of patients reported viral infections while on rituximab during CLL clinical trials. Herpesviridae accounted for 5% among these and hepatitis B accounted for a further 1.1%. Other 3.8% of patients reported serious viral infections, with Herpesviridae being the most common, followed by hepatitis B.

Fungal infections were reported in 3.6% patients, with *Candida* reported in 1.6% and *Pneumocystis jirovecii* reported in 0.7%. Serious fungal infections were reported in 1.3% patients, *Pneumocystis jirovecii* accounting for 0.7%.

Opportunistic infections were reported in 2.9% cases. The leading pathogens in this group were *Pneumocystis jirovecii* (5 cases) and *Aspergillus* (4 cases). No bacterial opportunistic infections were reported (DSR 1066792, dated March 2016).

Severity and nature of risk:

RA

In the All Exposure population, 72.6% (2611/3595) of patients experienced at least one infection. Infections observed in 5% of patients were upper respiratory tract infection (URTI, 26%), nasopharyngitis (18%), urinary tract infection (UTI, 17%), bronchitis (14%), diarrhoea (11%), sinusitis (12%), influenza (8%), gastroenteritis (7%), and pneumonia (5%). The majority of infections were mild to moderate in severity. Severe infections (CTC Grade 3) were reported in 8% of cases and were life threatening in < 1% and fatal in < 1%.

The rate of all infections was the highest during the first 12 months after administration of rituximab, decreased thereafter and remained stable across multiple treatment courses. Notably, the rate of serious infections was not higher during the first 12-month period after first exposure to rituximab than in the subsequent periods (DSR 1066792, dated March 2016). The rate and nature of all infectious events was similar over multiple treatment courses, with no evidence of an increased risk of infection with cumulative exposure to rituximab.

Seven serious opportunistic infections were reported in the All Exposure RA population, and one in the original placebo treatment-group.

GPA/MPA

Upper respiratory tract infections were the most commonly reported infections (8.1%, 8/99), followed by nasopharyngitis (6.1%), sinusitis (5.1%), UTI (5.1%), and pneumonia (4%), (DSR 1066792, dated March 2016).

Serious infections comprised mainly respiratory tract infections. The majority of patients experienced mild-to-moderate (Grade 1 or 2) infections.

Data from two investigator-sponsored studies of refractory/relapsing GPA/MPA, comparing the dose of 2x1000 mg vs. 4x375 mg/m2 (Jones et al. 2009 and Smith et al. 2012), are similar to the data from the RAVE study regarding the infection rate. The most frequently reported serious infections were respiratory tract infections (RTIs), as reported in RAVE.

Patients in RAVE were required to receive *Pneumocystis* prophylaxis. After 18 months, there had been a total of 2 non-serious opportunistic infections (*Mycobacterium avium* complex and oesophageal *Candida*) reported in the rituximab group.

In Study WA27893, from the 33 events of infections reported, 21 were Grade 3 to 5. The most commonly reported infection was pneumonia.

In Study ML22514, most of the infections reported were mild or moderate in intensity and were manageable. In the rituximab arm, the most commonly reported infections were bronchitis, nasopharyngitis, gastroenteritis and rhinitis.

In paediatric Study WA25615 (PePRS), during the overall study period, the majority of infection AEs (96 out of 105 AEs [91%]) were reported to be non-serious. Similar to the Remission Induction Phase, the most frequently reported infections during the overall study period were URTI (12 patients [48%]), all of which were non-serious.

Pemphigus Vulgaris

A total of 217 AEs were reported in the SOC Infections and infestations in the company safety database [DSR 1080390]. The most frequently reported to the Company Database (postmarketing) infectious PTs were nasopharyngitis, pneumonia, sepsis, infection and influenza. The nature of infectious AEs is in line with the known safety profile of the drug. Of all the AEs in the SOC, 51.6% (112/217) AEs were reported as serious. There were no reports of PML with rituximab for the pemphigus indication [DSR 1080390].

In Study WA29330 (PEMPHIX), the majority of infections were Grade 1 or 2 (five patients in the rituximab arm experienced grade 3 or higher infections). One patient in the rituximab arm had an infection that led to treatment interruption (Grade 1 oral herpes).

NHL/CLL

Patients with NHL or CLL are already at risk of infection due to their underlying disease. This risk is increased by the myelosuppressive effects of chemotherapy and radiotherapy, and the immunosuppressive effects of corticosteroids and particular cytotoxic agents (e.g., fludarabine). Damage to mucosal barriers (e.g., due to mucositis or diarrhoea) may also increase the risk of infection.

Serious viral infections including new infections, reactivation of latent infections and exacerbation of existing infections, some with a fatal outcome, have been reported in patients treated with rituximab. The majority of the patients had received rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant.

It is important to note that, in many patients with haematological malignancies who develop infections, a pathogen is never identified because of the need to institute broad spectrum antibiotic/antiviral therapy without delay.

NHL Induction Only (BO16368, M39021, M39045)

In the study population of the above-mentioned trials, 49% (384/778) of patients reported at least one infectious event; the pathogen was unspecified in 46% cases, and infections - not elsewhere classified (NEC) formed the largest group. Where classification was noted, bronchitis was commonest, being reported in 4.2%, followed by pneumonia (3.3%).

Other infections reported in more than 1% of patients included nasopharyngitis, sinusitis, URTI, lower respiratory tract infection (LRTI), neutropenic infection, and UTI.

The percentage of patients reporting Grade 3 infections stood at 12% (96/778). Where information was available regarding the specific infection, pneumonia formed the largest group among severe infections with 1.6%, LRTI and Herpesviridae were reported in 0.6% each. In 12 cases (1.5%) the infectious event was associated with fatality (DSR 1066792, dated March 2016).

NHL Induction and Maintenance (E1496, E 4494, M39022)

In the study population of the above-mentioned studies, 60% (547/917) of the patients administered rituximab reported at least one infectious event. The pathogen was unspecified in 56% cases, and infections-NEC again formed the largest group. Where classification was noted, URTI was the commonest reported at 3.7%, followed by neutropenic infection at 3.2%. Other infections reported in > 1% of patients include bronchitis, LRTI, nasopharyngitis, pharyngitis, pneumonia, RTIs, rhinitis, sepsis, sinusitis and UTI.

The percentage of patients reporting Grade 3 infections stood at 18% (161/917). Where classification was noted, neutropenic infection was reported most (3.2%), followed by sepsis (1.3%), and pneumonia (1.1%). In 12 cases (1.3%) the infectious event had a fatal outcome (DSR 1066792, dated March 2016).

NHL Maintenance Only (MO18265)

In the PRIMA study, 44% (220.501) of patients reported at least 1 infectious event while on rituximab maintenance therapy. The pathogen was unspecified in 43% cases, with infections-NEC constituting the largest fraction. Where classification of infection was noted, bronchitis was the commonest at 11%, followed by URTI at 5.8%. Other infections that were reported in > 1% of

patients included lung infection, nasopharyngitis, neutropenic infection, pharyngitis, pneumonia, RTI, rhinitis, sinusitis, and UTI.

The percentage of patients reporting > Grade 3 infections stood at 4.8% (24/501). No specific site/type of infection stood out. Infection had a fatal outcome in 2 cases, including one case of PML (DSR 1066792, dated March 2016).

Paediatric B-NHL (BO25380)

Infections were common during the overall treatment period of the study, occurring in 52.3% of subjects in the chemotherapy arm and 62.3% of subjects in the chemotherapy plus rituximab arm. The most common infections (10%) reported in the chemotherapy plus rituximab arm were sepsis (17.9%), device-related infection (13.0%) and lung infection (13.0%). Grade > 3 infections were reported in 19.1% of subjects in the chemotherapy plus rituximab arm (primarily events of sepsis). Three (1.2%) of the events in the chemotherapy plus rituximab arm were fatal (all events of sepsis).

CLL (BO17072, ML17102)

Thirty-three percent of patients (226/676) in CLL clinical trials reported at least one infectious event. The pathogen was unspecified in 24% cases. Where infection classification was noted, bronchitis was the commonest reported at 3.6%, followed by pneumonia at 3.5% and URTI at 3.4%. Other infections which were reported in > 1% of patients included nasopharyngitis, RTI, sepsis and sinusitis.

The percentage of patients reporting Grade 3 infections was 18% (121/676). The most common reported infection in this group was pneumonia (4.0%), followed by sepsis and bronchitis (1.5% each). Infectious events led to fatality in 22 cases (3.3%), (DSR 1066792, dated March 2016).

Opportunistic infections are infections occurring in a compromised host, which are caused by microorganisms that normally do not cause serious disease in healthy people.

A range of organisms can cause opportunistic infections and these overlap with non-opportunistic infections (which occur in healthy individuals), neutropenic infections, and reactivation of latent viral infections. Opportunistic infections range in severity from mild to life-threatening or fatal. Commonly recognized serious opportunistic infections include viruses (Cytomegalovirus [CMV], Varicella Zoster, Herpes Simplex and John Cunningham [JC] viruses), fungi (*Pneumocystis jirovecii pneumonia*, *Aspergillosis*, some *Candida* infections, cryptococcal infections and *coccidioidomycosis*), bacteria [*Mycobacterium avium* complex infections and *Mycobacterium* tuberculosis] and protozoa [*Cryptosporidium* and *Toxoplasma infections*]).

Seriousness/Outcomes:

Serious infections for oncology and GPA/MPA trials were defined as those infections which resulted in death, a life-threatening event, hospitalization or prolongation of hospitalization, persistent or significant disability, or a congenital anomaly/birth defect. For RA trials, serious infections were defined as those which were reported as SAEs or required treatment with an IV anti-infective.

RA

In the All Exposure population (all data, irrespective of treatment course) 415/3595 (11.5%) patients experienced a total of 532 serious infections following treatment with rituximab, with an overall rate of 3.76 per 100 patient-years (95% CI: 3.46;4.09), 2.71/100 patient-years in patients observed for > 5 years. This is comparable with placebo populations (3.79; CI: 2.80; 5.13) and also with rates reported previously in rituximab-treated patients at 9.5 years observation (3.94/100 patient-years and 3.26/100 patient-years, respectively), (DSR 1066792, dated March 2016).

The rate of serious infections was stable across time periods and also between multiple courses of rituximab treatment. There was no evidence of an increased risk of serious infection with cumulative exposure to rituximab.

Table 5Table 5 displays the rates of serious infections by treatment course over the first 7 courses, and Table 6 displays a summary of the serious infections reported in at least 5 patients.

Table 5 Summary of Rate of All Serious Infections per 100 Patient Years (All Exposure RA Population)[1]

Incidence rates	All Exposure Population (N =3595)	First Course (N = 3595)	Second Course (N = 2752)	Third Course (N = 1744)	Fourth Course (N = 1471)	Fifth Course (N = 1202)	Sixth Course (N = 906)	Seventh Course (N = 709)
Total Patient-years	14816	3957	3586	1947	1596	1216	834	615
Number of Serious Infections	532	160	129	67	61	58	26	15
Serious Infections Per 100 Patient-years	3.76	4.0	3.6	3.4	3.8	4.8	3.1	2.4
95% CI for Rate Per 100 Patient-years	3.5:4.1	3.5:4.7	3.0:4.3	2.7:4.4	3.0:4.9	3.7:6.2	2.1:4.6	1.5:4.0

[1]Data cut-off: September 2012.
Table includes all events reported as serious and/or treated with IV Antibiotics.

Table 6 Summary of Serious Infections Reported in 5 Patients (All Exposure Rheumatoid Arthritis Population) (MabThera)

Body System/ Adverse Event	All Exposure Population N = 3595 No. (%)
ALL BODY SYSTEMS	

Body System/ Adverse Event	All Exposure Population N = 3595 No. (%)
Total pts with at least one AE	415 (12)
Total number of AEs	532
INFECTIONS AND INFESTATIONS	
Total PTs With at Least One AE	381 (11)
Pneumonia	76 (2)
Cellulitis	39 (1)
Urinary tract infection	35 (< l)
Gastroenteritis	23 (< l)
Bronchitis	17 (< l)
Diverticulitis	13 (< l)
Lower respiratory tract infection	13 (< l)
Bronchopneumonia	12 (< l)
Appendicitis	11 (< l)
Pyelonephritis	11 (< l)
Sepsis	11 (< l)
Pyelonephritis acute	9 (< l)
Urosepsis	9 (< l)
Arthritis bacterial	8 (< l)
Respiratory tract infection	7 (< l)
Clostridium difficile colitis	6 (< l)
Infection	6 (< l)
Postoperative wound infection	5 (< l)
Sinusitis	5 (< l)
GASTROINTESTINAL DISORDERS	
Total PTs With at Least one AE	15 (< l)
Diarrhoea	8 (< l)

Investigator text for Adverse Events encoded using MedDRA version 15.0. Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
** Reported as serious and/or treated with IV Antibiotics.
Includes placebo data from patients treated with Rituximab who then received placebo as retreatment
Imputed start dates were used to identify whether the adverse event was treatment emergent.
Terms were identified by using the Infections AEGT and the identifying tick box on the adverse event page for studies U3374G, U3384G, U3924G, WA17044, WA17045 and WA17047 AE11 20NOV2012:13:09:42
Source: staellsifc_a

With the exception of the 15 deaths, the majority of infections (non-serious and serious infections) followed a typical course and were successfully treated with standard antibiotics.

The most frequently reported serious infections in the All-Exposure population were lower respiratory tract infection (LRTI; 3%, 114 patients), predominantly pneumonias (2.7%, 96 patients). Of the 11.5% patients who reported serious infections, 8% reported no specific pathogen, 2% reported bacteria and < 1% reported viruses and fungi each (DSR 1066792, dated March 2016).

In the All Exposure RA population, 7 serious opportunistic infections were reported. These included 2 cases of atypical pneumonia (no organisms isolated) and one case each of *Candida* septicaemia, pharyngeal abscess (organism unspecified), *Scedosporium* lung infection, PJP (leading to withdrawal) and PML (with fatal outcome). One event of PJP occurred in the placebo population. Among other infections, one case of *de novo* Hepatitis B Virus (HBV) infection occurred in the All Exposure population, as well as 2 cases of pulmonary tuberculosis (TB), both treated with a course of standard anti-TB medication. There were no reported cases of extrapulmonary TB, atypical Mycobacterial infection or multidrug-resistant TB (DSR 1066792, dated March 2016).

Fifteen serious infections (< 1%) in the All Exposure population resulted in death. Seven fatal cases were from respiratory infections, 6 from septic events (including septic shock) and one patient each died from *C. difficile* colitis and PML. No apparent relationship between time of event onset and time since the first rituximab dose was identified (range of 145 to 2886 days). Four of the fifteen serious infection events with fatal outcome were assessed as related to the study treatment (2 events of septic shock, and one each of sepsis and PML); while other events were assessed as not related to the study treatment (DSR 1066792, dated March 2016).

GPA/MPA

In the RAVE study, the proportions of rituximab patients experiencing a serious or severe (Grade 3) infectious adverse event groups at 6 months was 11.1% (11/99 patients) for serious infections and 10.1% (10/99 patients) for severe infectious events. No infection events were reported as fatal in rituximab treated patients. By 18 months, the incidence of serious infections was 15.2%. The incidence of serious infections reported in rituximab-treated patients were consistent with those observed with the control arm (cyclophosphamide) treatment, where the incidence of serious infections was 15.3%.

Similarly, the incidence of severe infections was comparable at 13.1% for the rituximab and 13.3% for the cyclophosphamide group at 18 months.

Given the small number of serious and/or severe infectious events reported, no single organism (bacterial, viral or fungal) stood out from the data (DSR 1066792, dated March 2016).

The 2 opportunistic infections that were reported in the RAVE study were non-serious.

In Study WA27893, fourteen patients had 24 serious infections with the most reported terms being gastroenteritis, influenza, pneumonia and staphylococcal bacteraemia. One patient died due staphylococcal bacteraemia and septic shock.

In Study ML22514, the incidence of serious infections was similar between the two treatment arms (12.3% rituximab vs 12.1% azathioprine) and the most commonly reported serious infection in the rituximab arm was bronchitis. A total of three opportunistic infections were reported in study ML22514 (all serious); two patients in the rituximab arm experienced one event each of severe oesophageal candidiasis and moderate PJP, and one patient in the azathioprine arm experienced moderate atypical mycobacterial pneumonia. One patient in the azathioprine arm died due to infection versus none in the rituximab arm.

In the DSR 1081144 (data cut-off date: 03-Mar-2017) the following serious infections were reported in the MabThera global safety database; pneumonia (n=18), infection (not otherwise specified, n=13), LRTI (n=7), pneumonia bacterial (n=6) and sinusitis (2).

In paediatric Study WA25615 (PePRS), during the Overall Study Period, 105 infection AEs were reported in 23 patients (92%) of which the majority (96 out of 105 AEs [91%]) were reported to be non-serious. Similar to the Remission Induction Phase, the most frequently reported infections during the overall study period were upper respiratory tract infections (12 patients [48%]), all of which were non-serious.

Pemphigus vulgaris

In Study ML22196, 3 patients (7.9%) from the rituximab + prednisone arm experienced 5 serious infections. In the prednisone arm, one patient (2.8%) experienced one serious infection. The PTs for serious infections (rituximab + prednisone arm vs. prednisone) were *Pneumocystis jirovecii* pneumonia (one patient in each treatment arm), infective thrombosis (one patient vs. 0 patients), intervertebral discitis (one patient vs. 0 patients), lung infection (one patient vs. 0 patients), and staphylococcal sepsis (one patient vs. 0 patients).

In Study WA29330 (PEMPHIX), in the rituximab arm, 42 patients (62.7%) experienced 74 infections. In the rituximab arm, infections reported in 5% of patients were upper respiratory tract infection (7 patients, 10.4%), nasopharyngitis and oral candidiasis (6 patients each, 9.0%) and urinary tract infection (5 patients, 7.5%).

NHL/CLL

Serious infections are a major cause of morbidity and mortality in patients with haematological malignancies and are a frequent complication of treatment. Infections are often severe, requiring rapid diagnosis and aggressive antibiotic treatment, and infection is often the ultimate cause of death in patients with refractory, progressive haematological malignancies such as CLL or NHL.

Opportunistic infections are a major cause of morbidity and mortality in immunosuppressed patients, including cancer patients receiving chemotherapy, organ transplant recipients, and patients with human immunodeficiency virus (HIV) infection.

NHL Induction Only (8016368, M39021, M39045)

Serious infections were reported in 11% of patients (86/778). In 7.7% of cases, no infectious agent was specified. Fatal infections accounted for 1.5% of cases (12/778). Two patients died due to bacterial infections and one died from *Candida* sepsis. No fatal viral infections were noted.

Serious bacterial infections were reported in 2.6% cases. *Staphylococcus spp.* accounted for 1% and *E. coli* for another 0.4% of these.

Serious viral infections were reported in 1% cases with Herpesviridae accounting for half of these (0.5%).

Serious fungal infections were reported in only 3 cases, accounting for 0.4%; these were also the only serious opportunistic infections reported. No specific pathogen stood out (DSR 1066792, dated March 2016).

NHL Induction and Maintenance (E1496, E 4494, M39022)

Serious infections were reported in 7.7% (71/917) of patients. In 6.5% patients, the pathogen was unspecified. Infections were fatal in 1.3% of cases. One patient died due to pulmonary mycosis. No causative agent was specified in the other fatal cases.

Serious bacterial infections were reported in 1.2% of patients (11 in number). No specific prominent bacterial pathogen stood out.

Serious viral infections were reported in 1.2% of patients (10/917) and in these studies too, Herpesviridae were the most commonly reported pathogen, accounting for half the reported serious viral infections.

Serious fungal infections were reported in 1.0% of patients (9/917). *Candida spp.* were the largest group, accounting for 0.6% of the reports. One case of PJP was reported.

Serious opportunistic infections were reported in 2 cases, one of PJP and the other with pulmonary mycosis (DSR 1066792, dated March 2016).

NHL Maintenance Only (MO18265)

Serious infections were reported in 5.2% (26/501) of patients who received maintenance rituximab in the MO18265 study. 0.4% (2/501) of patients had a fatal infectious event, which included one case of PML. No fatal bacterial or fungal infections were noted.

Serious bacterial infections were reported in 0.4% of cases. No specific pathogen stood out.

Serious viral infections were reported in 6 of cases, which included 2 cases of hepatitis B. No serious fungal infections were noted.

Two serious opportunistic infections were reported, one case of PML and one of mycobacterial infection (DSR 1066792, dated March 2016).

CLL (BO17072, ML17102)

Eighteen (18) % (125/676) of the patients receiving rituximab for CLL in clinical studies reported a serious infection. In most cases the pathogen was not specified. 3.3% of patients had fatal infectious events. Sepsis and respiratory tract infections (RTIs) accounted for a major share of

fatalities where the pathogen was not specified. Viral infections (including 2 cases of hepatitis B) were associated with 6 fatal events and aspergillosis was associated with one fatal event. No fatal bacterial infections were noted.

Serious bacterial infections were reported in 1.8% (12/676) cases. No specific pathogen stood out.

Serious viral infections were reported in 3.8% (26/676) of cases with Herpesviridae accounting for almost half of these (12 cases) and hepatitis B accounting for another 6.

Serious fungal infections were reported in 1.3% (9/676) of patients and included 2 cases of PJP and 2 cases of aspergillosis.

Serious opportunistic infections were reported in 2.0% of patients and mainly comprised *Pneumocystis* and *Aspergillus*. Two serious CMV infections were also reported (DSR 1066792, dated March 2016).

Reversibility:

Infections are a frequent complication of treatment and major cause of morbidity and mortality in patients with haematological malignancies. Many infections occurring in immunocompromised patients can be cured, although opportunistic fungal and viral infections typically are associated with high morbidity and mortality, and may require long-term treatment to prevent relapse. The majority of infections occurring in patients receiving rituximab for RA and GPA/MPA are non-serious and are successfully cured with standard anti-infective agents (see further information in risks of PML). The extent of reversibility depends on the pathogen. Many infections caused by common respiratory and enteric viruses are likely to resolve completely without long-term sequelae, and require only supportive treatment. Others may require antiviral therapy (e.g., HSV, CMV). Hematogenous bacterial and fungal infections require hospitalization and aggressive treatment, and are associated with substantial morbidity and mortality, although complete resolution can be expected in patients who survive. Some opportunistic viral infections are irreversible (see further information of risks of PML, Hepatitis B Reactivation).

Impact on quality of life:

Although the impact on patient quality of life depends on the specific pathogen, many infections in immunocompromised patients are life threatening or require prolonged hospitalization and anti-infective therapy. Serious viral infections like encephalitis can be associated with significant morbidity and mortality. Most opportunistic infections are associated with substantial morbidity and mortality. Some are irreversible and/or associated with serious long-term sequelae, disability and dependence. Depending on the seriousness of the infection, the increased chance of hospitalization and extended antibiotic therapy, the impact of infection on quality of life can be substantial.

Risk factors and risk groups:

RA and GPA/MPA

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). The HR for the development of objectively confirmed infections in RA patients compared with non-RA patients, after adjustment for confounding variables, was 1.70. Within RA patients, increasing age, presence of extra-articular manifestations of RA, and co-morbidities, as well as use of corticosteroids, were strong predictors of infection risk. The predicting co-morbidities were chronic lung disease, chronic kidney disease, alcoholism, organic brain disease, and diabetes mellitus. Of the disease-modifying therapies examined, corticosteroids consistently increased infection risk. In large studies, infection rates are clearly increased with cyclophosphamide or azathioprine, whereas MTX appears to be associated with minimal, if any, increased infection risk (McLean-Tooke et al. 2009). Data about other DMARDs are scarce, and the main cause of therapy withdrawal is related to toxicity rather than infection (Iaccarino et al. 2007). Anti-TNF-a agents like IFX are associated with an increased risk for TB, HBV reactivation and opportunistic infections (OIs), (Botsios 2005).

Risk factors for infection in GPA/MPA patients include the concomitant use of high dose corticosteroids and/or other immunomodulatory agents.

Pemphigus vulgaris

None.

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. In a retrospective analysis by (Bishop et al. 1981), a higher infection rate in NHL patients was associated with granulocytopenia and post splenectomy. The commonest sites of infection were lung, skin, and alimentary canal. Risk factors for infections identified in the literature in patients with CLL include advanced disease stage, previous antineoplastic therapy, refractoriness to fludarabine-based therapy, high serum B2-microglobulin level, low serum albumin level, low granulocyte count and high serum creatinine concentration (Anaissie et al. 1998).

The risk of serious viral infection/reactivation is mainly related to concomitant chemotherapy and the patient's underlying condition. Fludarabine in particular has been associated with an increased risk of serious viral infections including CMV and JC virus/PML, and this is probably related to the induction of profound CD4+ lymphopenia.

The risk of developing PJP among HIV patients rises markedly when circulating CD4+ cell counts fall below 200/µL. A low CD4+ count is likely to be a major risk factor for opportunistic infections in other patients including those receiving immunosuppressive therapy (particularly glucocorticoids) for haematological malignancies such as NHL or CLL.

Patients with CLL are predisposed to common as well as opportunistic infections as a result of a number of disease-related factors including immunoglobulin deficiency, abnormal T-cell function, and neutropenia resulting from infiltration of the bone marrow.

Preventability:

RA and GPA/MPA

The rituximab SmPC includes information pertaining to minimizing the risk of infections. Based on the mechanism of action of rituximab and the knowledge that B-cells play an important role in maintaining normal immune response, patients may have an increased risk of infection following rituximab therapy. Serious infections, including fatalities, can occur during therapy with rituximab. Rituximab should not be administered to patients with an active severe infection (e.g., tuberculosis, sepsis and opportunistic infections) or severely immunocompromised patients (e.g., where levels of CD4 or CD8 are very low). Physicians should exercise 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 e.g., hypogammaglobulinaemia. It is recommended that immunoglobulin levels are determined prior to initiating treatment with rituximab. PJP prophylaxis is recommended for patients with GPA/MPA during and following rituximab treatment, as appropriate.

Information to inform patients on the risks of PML and infections in RA and GPA/MPA has been developed as an additional risk minimization activity. This information is summarized in the Patient Alert Card (PAC).

NHL/CLL

The increased risk of infection associated specifically with administration of rituximab (if it occurs) cannot be prevented and no specific measures are recommended for rituximab itself. Rituximab should not be administered to patients with an active infection or severely immunocompromised patients (e.g., where levels of CD4 or CD8 are very low). Physicians should exercise 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.

Primary prophylaxis for PJP with cotrimoxazole and for viral infection with agents such as acyclovir is not generally indicated for patients with NHL or CLL treated with rituximab. However, it may be indicated for the concomitant chemotherapy e.g., patients receiving fludarabine-based regimens (regardless of whether rituximab is given).

Patients reporting signs and symptoms of infection following rituximab therapy should be promptly evaluated and treated appropriately. Before giving a subsequent course of rituximab treatment, patients should be re-evaluated for any potential risk for infections. Physicians should exercise 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.

Indications for primary prophylaxis against opportunistic infections are not clear for patients with haematological malignancies, including patients with NHL or CLL treated with rituximab-containing regimens. Primary prophylaxis (with trimethoprim/sulphamethoxazole ± antivirals) is probably indicated for patients receiving fludarabine-based regimens (regardless of whether rituximab is given).

Impact on the benefit-risk balance of the product:

No new aspects of the important identified risk of Infections, including serious infections, has become available to the Marketing Authorisation Holder (MAH) in any indications to date. The benefit-risk profile of rituximab in the approved indications remains unchanged and favourable.

Public health impact:

No public health impact in view of the population treated and the limitations placed upon administration of rituximab by virtue of the warnings and precautions and its formulation. Use outside of controlled environments by non-HCPs is not anticipated.

1.2 PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (ALL INDICATIONS)

Potential mechanisms:

Rituximab's mechanism of action induces B-cell depletion that can lead to a depressed immune system. In addition, previous or concomitant immunotherapy, bone marrow infiltration, and/or corticotherapy might be important contributing factors of reactivation of latent JC virus.

Further for NHL/CLL, the underlying malignancy can also contribute to immunosuppression.

Evidence source(s) and strength of evidence (from reference medicinal product MabThera data):

- MabThera SmPC
- DSR 1096921 Progressive Multifocal Leukoencephalopathy (PML) Cumulative update report for Rituximab, dated January 2019 (cut-off 17 November 2019)
- DSR 1091848 PML annual update report (cut-off 17 September 2018)
- 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 (cut-off 17 November 2016)
- DSR 1066994 Progressive Multifocal Leukoencephalopathy (PML) Cumulative update report for Rituximab, dated 12 January 2016 (cut-off 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 July2011)
- Six more cumulative updates: 1042104, 1047784, 1050172, 1053546, 1058316, and 1062808 (cut-off 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 (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
- 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

Characterization of the risk:

Frequency with 95% Confidence Interval (CI): (MabThera)

RA

Confirmed PML is very rare (< 1/10,000 patients) in patients receiving rituximab for the treatment of RA, based on all data from clinical and postmarketing experience. The cumulative (cut-off 17 November 2020) reporting rate of 20 confirmed PML cases in patients treated with rituximab for RA is 2.06 per 100,000 unique patients (RA exposure ~ 969,416). Eleven out of the 20 confirmed cases of PML resulted in fatal outcome.

GPA/MPA

Confirmed PML is very rare (< 1/10,000) in patients receiving rituximab for the treatment of GPA/ MPA. In the cumulative period until 17 November 2020, an estimation of 96,653 patients were exposed to rituximab in GPA/MPA, and only 5 confirmed PML cases in GPA/MPA were reported.

No events of PML were reported in studies WA27893 and ML22514, in DSR 1081144, and in paediatric study WA25615.

Pemphigus vulgaris:

No events of PML were reported.

NHL/CLL

The reporting rate of PML in oncology indications (confirmed and unconfirmed) is around 6.7/100,000 (390/5,757,196) patient exposures and remains very rare to rare, based on postmarketing experience and clinical trial data.

Severity and nature of risk:

PML is a rare progressive subacute-demyelinating disorder of the central nervous system (CNS) usually leading to death or severe disability. The severity of the PML was not reported in the majority of cases.

The majority of patients with a diagnosis of PML after treatment with rituximab reference product (across all indications), had not recovered at the time of reporting. Only in a few cases, the PML was resolving at the time of the last report.

Seriousness/Outcomes:

A cumulative multiaxial search of PML events and PML confirmatory tests was carried out covering all the data for rituximab in the company (MAH for reference product) safety database ARISg up to the cut-off date 17 November 2020.

RA

As of 17 November 2023, 24 cases of confirmed PML have been reported in patients treated for RA, of which 13 cases had a fatal outcome. Seventeen out of 24 confirmed cases reported in RA were reported in female patients, which is representative of the autoimmune patient population. Of the 24 confirmed PML cases, 19 patients had significant known risk factors for PML. All 19 patients had received significant prior and/or concomitant immunosuppressant therapy including DMARDS and TNF inhibitors

GPA/MPA

As of 17 November 2023, 9 cases of confirmed PML have been reported in patients with GPA/MPA. Considering the 9 confirmed PML cases in GPA/MPA and the cumulative exposure of 111,538

patients, the reporting rate is 8.0 per 100,000 patients and remains very rare. In 6 out of the total 9 cases, the patient had significant known risk factors for PML including concomitant immunosuppressive therapy predominantly cyclophosphamide, epirubicin, fluorouracil, methotrexate, azathioprine and prednisolone or had concomitant condition of polyarthralgia or underlying lymphoproliferative disease, systemic AI disease or primary immunodeficiency. In one case, prior to the start of rituximab, the patient had signs of PML which were reported as deficiencies in higher cognitive functions. In addition, this patient had a medical history of breast cancer and also had received significant prior and concomitant immunosuppressive therapy. In the remaining two literature cases, there was limited information reported for adequate assessment..

Pemphigus Vulgaris:

No information available.

NHL/CLL

As of 17 November 2023, 293 cases of confirmed PML have been reported in patients treated for underlying NHL, of which 149 cases have thus far had a fatal outcome. Also, 149 cases of confirmed PML have been reported in patients treated for underlying CLL, of which 71 cases have thus far had a fatal outcome.

The majority of the patients who developed PML under rituximab therapy for NHL indications were receiving concomitant cytotoxic chemotherapy (predominantly CHOP). In a few cases, the information regarding concomitant chemotherapy was not reported. The patients also had pertinent alternative causes (past medical history like HIV, IRIS, Sjogren's syndrome, past drugs and concomitant drugs like chlorambucil, fludarabine, steroids) of underlying immunosuppression.

The majority of the patients who developed PML under rituximab therapy for CLL indications were receiving concomitant cytotoxic chemotherapy (predominantly fludarabine) or were immunosuppressed intentionally following stem cell transplant. In addition, the majority of the patients were receiving steroids. In a few cases, the information regarding concomitant chemotherapy was not reported. The patients also had pertinent alternative causes of underlying immunosuppression.

Reversibility:

There is currently no treatment available for PML, although disease progression has been slowed or halted in some patients by withdrawal of treatment.

Impact on quality of life:

PML causes gradual, progressive CNS demyelination, multifocal neurological deficit, and death, usually within one year. Hence, the impact on quality of life is substantial.

Risk factors and risk groups:

RA

PML has been reported in patients with autoimmune diseases including systemic lupus erythematosus (SLE) and RA who have received immunosuppressive agents.

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 humeral 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.

A close evaluation of rituximab associated cases of PML found that most cases occurred in individuals with a well-known concomitant risk of PML such as prior or concurrent exposure to a recognized immunosuppressant. In NHL/CLL, PML occurred at any time after rituximab treatment. although after 12 - 24 months the frequency of PML was lower (DSR 1081270; dated 28 June 2017).

Preventability:

There are no approved treatments available to prevent, retard, stop, or reverse the disease once established in patients.

Impact on the benefit-risk balance of the product:

No new aspects of the important identified risk PML have become available to the MAH in any indications to date. The benefit-risk profile of rituximab in the approved indications remains unchanged and favourable.

Public health impact:

RA, GPA/MPA and PV

Limited public health impact in view of the population treated and the limitations placed upon administration of rituximab by virtue of the warnings and precautions and its formulation. Use outside of controlled environments by non-HCPs is not anticipated. The MAH continues to monitor for any such occurrences.

NHL/CLL

None. There is no reason to suppose that PML occurring in a patient receiving rituximab would have any public health implications since JC virus infection is ubiquitous and the disease is caused by reactivation of a latent form.

INFORMATION ON IMPORTANT POTENTIAL RISKS

No important potential risks for IV formulation.

SVII.3.2 Presentation of the Missing Information

None.

Part II: Module SVIII - Summary of the safety concerns

The summary of the safety concerns for Ituxredi is based on the European Union (EU) RMP for MabThera® (rituximab) version 25.1 dated 21 October 2024 published on the European Medical Agency website.

Table 7 Summary of Safety Concerns

Summary of Safety Concerns	
Important Identified Risks	• Infections, including serious infections (All Indications) • Progressive multifocal leukoencephalopathy (All Indications)
Important Potential Risks	• None
Missing Information	• None

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for:

None

Other forms of routine pharmacovigilance activities for pregnancy and/or breastfeeding:

The DRL standard pregnancy follow-up process was implemented for all products to request additional information on the medication history of the exposed parent, relevant medical history for the mother and father, previous obstetric history, the current pregnancy, fetal and infant conditions, and results of tests and investigations for any pregnancy complication or congenital abnormality during pregnancy or within the first year of the infant's life.

III.2 Additional pharmacovigilance activities

Routine pharmacovigilance activities are considered sufficient and no additional pharmacovigilance activities are considered necessary for Ituxredi.

III.3 Summary Table of additional Pharmacovigilance activities

There are no ongoing or planned additional pharmacovigilance activities being conducted for Ituxredi.

Part IV: Plans for post-authorisation efficacy studies

Not applicable.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

The safety information in the proposed product information is aligned to the reference medicinal product.

V.1 Routine Risk Minimisation Measures

Table 8 Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Important Identified Risks	
Infections, including serious infections **All Indications**	**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**

Safety Concern	Routine Risk Minimization Activities
	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
Progressive Multifocal Leukoencephalopathy **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:** 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, 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 rituximab must be permanently discontinued. **Other risk minimization measures beyond the Product Information:** *Medicine's legal status:* Medicinal product subject to restricted medical prescription.
Important Potential Risks	
None	
Missing Information	
None	

V.2 Additional Risk Minimisation Measures

Table 9 Safety Concern: Infections, Including Serious Infections

Additional Risk minimization Measure	**Patient Alert Card** (non-oncology indications)
Objectives	The objective is to provide patients with important safety information to ensure that patients seek medical attention early, to facilitate timely diagnosis of infections generally, and PML in particular.
Rationale for the additional risk minimization activity	The rationale is that with timely diagnosis of infections, continued treatment with rituximab can be evaluated and reductions or discontinuation of concomitant immunosuppressive therapy considered.
Target audience and planned distribution path	**Patient Alert Card (PAC):** Target audience: Patients To be distributed in-carton alongside the package leaflet.
Plans for evaluating the effectiveness of the interventions and criteria for success	How effectiveness of risk minimization measures for the safety concern will be measured: Effectiveness will be assessed using both process and outcome indicators. Process indicator: The distribution of the PAC will be agreed with local health authority before launching the product which could be active by distributing with the packaging of the product or via MAH website. Outcome indicator: Total Individual Case Safety Reports reported during the PSUR periods will be evaluated. Criteria for judging the success of the proposed risk minimization measures: Distribution of material at affiliate level before launch will be used as an indicator of success of the overall process. Planned dates for assessment: Outcome is measured at the data lock point for each scheduled PSUR (PBRER) for rituximab.

Table 10 Safety Concern: Progressive Multifocal Leukoencephalopathy

Additional Risk	**Patient Alert Card** (non-oncology indications)

Minimization Measure	
Objectives	The objective is to provide patients with important safety information to ensure that patients seek medical attention early, to facilitate timely diagnosis of PML.
Rationale for the additional risk minimization activity	The rationale is that with timely diagnosis of PML, treatment with rituximab can be discontinued and reductions or discontinuation of concomitant immunosuppressive therapy considered.
Target audience and planned distribution path	**Patient Alert Card (PAC):** Target audience: Patients To be distributed in-carton attached to the package leaflet.
Plans for evaluating the effectiveness of the interventions and criteria for success	How effectiveness of risk minimization measures for the safety concern will be measured: Effectiveness will be assessed using only process indicator. Process Indicator: The distribution of the PAC will be agreed with local health authority before launching the product which could be active by distributing with the packaging of the product or via MAH website. Outcome indicator: Given the very low incidence of PML, and given that the purpose of the education material is to raise awareness of PML among patients and physicians, to encourage early recognition and diagnosis, it is not possible to directly measure whether the material has an effect on patient outcome. Criteria for judging the success of the proposed risk minimization measures: Distribution of material at affiliate level before launch will be used as an indicator of success of the overall process. Planned dates for assessment: Outcome is measured at the data lock point for each scheduled PSUR (PBRER) for rituximab.

Removal of additional risk minimisation activities

Rationale for removal of additional risk minimization measures

Updated inline with the reference medical product RMP.

V.3 Summary of Risk Minimisation Measures

Table 11 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Infections, including serious infections **All Indications**	**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:** Patient Alert Card (non-oncology indications)	**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 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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	PML has been excluded. Further evaluations, including Magnetic Resonance Imaging scan preferably with contrast, CSF testing for JC Viral DNA and repeat neurological assessments, should be considered. If a patient develops PML, the dosing of rituximab 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)	

BIBLIOGRAPHY

Abdel-Nasser AM, Rasker JJ, and Vaikenburg HA. Epidemiological and clinical aspects relating to the variability of rheumatoid arthritis. Semin Arthritis Rheum 1997;27:123-140.

Aladjidi N, Leverger G, Leblanc T, et al: New insights into childhood autoimmune hemolytic anemia: a French national observational study of 265 children. Haematologica 96:655-63, 2011

Alhashimi M and Pittelkow M. Epidemology of pemphigus in olmsted county, minnesota from 1950-2000. J Am Acad Dermatol. 2005.[11004]

Alireza Firooz, MD1, Adil Mazhar, BS1, A. Razzaque Ahmed, MD, DSc'Correspondence information about the author MD, DSc A. Razzaque Ahmed1 Boston, Massachusetts, USA. Prevalence of autoimmune diseases in the family members of patients with pemphigus vulgaris, Department of Dermatology, Boston University School of Medicine. September 1994Volume 31, Issue 3, Part 1, Pages 434–437 [11243].

Aljary H, Czuzoj-Shulman N, Spence AR, Abenhaim HA. Pregnancy outcomes in women with rheumatoid arthritis: a retrospective population-based cohort study. J Matern Fetal Neonatal Med. 2020 Feb;33(4):618-624.

Ambinder AJ, Shenoy PJ, Malik N, Maggioncalda A, Nastoupil LJ, Flowers CR. Exploring risk factors for follicular lymphoma. Adv Hematol. 2012;2012:626035

Anaissie EJ; Kontoyiannis DP, O'Brien S, Robertson L; Susan Lerner S, Keating MJ et al. Infections in patients with chronic lymphocytic Leukemia treated with fludarabine. Clinical Rev 1998;129(7):559-566. Web ref: http://www.annals.org/cgi/content/ful1/129/7/559).

Animesh A.SinhaMD, PhD Dermatologic Clinics, Volume 29, Issue 3, July 2011, Pages 381-391 The Genetics of Pemphigus. [11244]

Ansar Ahmed S, Dauphinee MJ, Talal N. Effects of short-term administration of sex hormones on normal and autoimmune mice. J Immunol 1985; 134:204.

Aringer M, Burkhardt H, Burmester GR et al. Current state of evidence on ‘off-label’ therapeutic options for systemic lupus wrythematosus, including biological immunosuppressive agents, in Germany, Austria and Switzerland – a consensus report. Lupus 2012) 21:386–401

Arnold et al. New treatments for idiopathic thrombocytopenic purpura: rethinking old hypotheses. Expert Opin. lnvestig. Drugs 2009; 18(6): 805-819.

Askling J, Fahrbach K, Nordstrom B, Ross S, Schmid CH, Symmons D. Cancer risk with tumor necrosis factor alpha (TNF) inhibitors: meta-analysis of randomized controlled trials of adalimumab, etanercept, and infliximab using patient level data. Pharmacoepidemiol Drug Saf 2011;20:119-130.

Baecklund E, et al. Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid Arthritis. Arthritis Rheum 2006;54:692-701#.

Baican A, Baican C, Chiriac G, et al. Pemphigus vulgaris is the most common autoimmune bullous disease in Northwestern Romania. Int J Dermatol. 2010;49:768-774. [11007]

Banwell B, Kennedy J, Sadovnick D et al. Incidence of acquired demyelination of the CNS in Canadian children. Neurol 2009;72:232-239.

Bennett CM, Rogers ZR, Kinnamon DD, Bussel JB, Mahoney DH, Abshire TC, et al. Prospective phase 1/2 study of rituximab in childhood and adolescent chronic immune thrombocytopenic purpura. Blood 2006;107(7):2639-2642

Bertram F, Brocker EB, Zillikens D, et al. Prospective analysis of the incidence of autoimmune bullous disorders in lower franconia, Germany. JDDG. 2009;7:434-439. [11010]

Bertsias et al. (EULAR/ERA-EDTA) recommendations for the management of adult and pediatric lupus nephritis. Ann Rheum Dis 2012;71:1771–1782.

Bishop JF, Schimpff SC, Diggs CH, et al. Infections during intensive chemotherapy for non-Hodgkin's lymphoma. Ann Intern Med. 1981 Nov;95(5):549-55.

Björnadal L et al. Decreasing mortality in patients with rheumatoid arthritis: Results from a large population based cohort in Sweden, 1964-95. J Rheumatol 2002;29:906-912.

Booth AD, Wallace S, McEniery CM, Yasmin, Brown J, Jayne DR, Wilkinson IB. Inflammation and arterial stiffness in systemic vasculitis: a model of vascular inflammation. Arthritis Rheum. 2004 Feb;50(2):581-8.

Botsios C. Safety of tumor necrosis factor and interleukin-1 blocking agents in rheumatic diseases Autoimmun. Rev. 4 (2005); 62-170.

Calabrese LH, Molloy ES, Huang D, Ransohoff RM. Progressive Multifocal Leukoencephalopathy in Rheumatic Diseases. Arthritis & Rheumatism 2007;56(7):2116-2128.

Casey RP-F, K. Raverdy, N. Forzy, M. L. Tretare, B. Carli, P. M. Maynadie, M. Casecontrol studyof lymphoid neoplasm in three French areas: Description, alcohol and tobacco consumption. European Journal of Cancer Prevention. April 2007;16(2):142-150
Catovsky D, Fooks J, Richards S. Prognostic factors in chronic lymphocytic Leukemia: the importance of age, sex and response to treatment in survival. A report from the MRC CLL 1 trial. MRC Working Party on Leukemia in Adults. Br J Haematol. 1989;72(2):141-149

Charles et al. Rituximab: Recommendations of the French Vasculitis Study Group (FVSG) for induction and maintenance treatments of adult, antineutrophil cytoplasm antibody-associated necrotizing vasculitides. Presse Med. 2013;42(10):1317-30.

Chu PG, Loera S, Huang Q, et al. Lineage determination of CD20– B-cell neoplasms: an immunohistochemical study. Am J Clin Pathol 2006;126:534-544.

Clowse ME, Richeson RL, Pieper C, Merkel PA; Vasculitis Clinical Research Consortium. Pregnancy outcomes among patients with vasculitis. Arthritis Care Res (Hoboken). 2013 Aug;65(8):1370-4.

Conter V, Rizzari C, Sala A, Chiesa R, Citterio M & Bondi A. Acute lymphoblastic leukemia. Orphanet Encyclopedia. December 2004. http://www.orpha.net/data/patho/GB/uk-ALL.pdf

Crowson CS, et al. The lifetime risk of adult-onset rheumatoid arthritis and other inflammatory autoimmune rheumatic diseases. Arthritis Rheum 2011; 63:633

Crowson CS1, Matteson EL, Myasoedova E, Michet CJ, Ernste FC, Warrington KJ, Davis JM 3rd, Hunder GG, Therneau TM, Gabriel SE. The lifetime risk of adultonset rheumatoid arthritis and other inflammatory autoimmune rheumatic diseases. Arthritis Rheum. 2011 Mar;63(3):633-9

Curtis JR et al. Risk of serious bacterial infections among rheumatoid arthritis patients exposed to tumor necrosis factor alpha antagonists. Arthritis Rheum 2007;56(4):1125-33.

Daneshpazhooh M, Chams-Davatchi C, Valikhani M et al. Pemphigus and pregnancy: a 23-year experience. Indian J Dermatol Venereol Leprol. 2011 Jul-Aug;77(4):534.

de Lind van Wijngaarden RA et al., Hypotheses on the etiology of antineutrophil cytoplasmic autoantibody associated vasculitis: the cause is hidden, but the result is known.Clin J Am Soc Nephrol. 2008;3(1):237. Epub 2007 Dec 12.

de Vries N, Tijssen H, van Riel PL, van de Putte LB. Reshaping the shared epitope hypothesis: HLA-associated risk for rheumatoid arthritis is encoded by amino acid substitutions at positions 67-74 of the HLA-DRB1 molecule. Arthritis Rheum 2002; 46:921

Denardo BA, Tucker LB, Miller LC, Szer IS, Schaller JG. Demography of a regional pediatric rheumatology patient population. Affiliated Children's Arthritis Centers of New England. J Rheumatol 1994;21:1553-1561

Dixon WG et al. Rates of serious infection, including site specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy. Arthritis Rheum.2006;54(8):2368-2376.

Doran MF et al. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. Arthritis Rheum 2002;46(9):2287-2293

Dores GM, Anderson WF, Curtis RE et al. Chronic lymphocytic Leukemia and small lymphocytic lymphoma: overview of the descriptive epidemiology. British Journal of Hematology 2007 139, 809–819.

Dreyling M, Ghielmini M, Marcus R, Salles G, Vitolo U, Ladetto M. Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2014:mdu200.

Egan G, Goldman S and Alexander S. Mature B-NHL in children, adolescents and young adults: current therapeutic approach and emergent treatment strategies. British Journal of Hematology. January 2019 (epub ahead of print).

El-Messidi A, Patenaude V, Abenhaim HA. Incidence and outcomes of women with nonHodgkin's lymphoma in pregnancy: a population-based study on 7.9 million births. J Obstet Gynaecol Res. 2015 Apr;41(4):582-9.

Eichhorst B, Robak T, Montserrat E, et al. Chronic lymphocytic Leukemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015;26(Suppl 5):v78–v84.

Eichhorst B et al. Chronic Lymphocytic Leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2021 Jan;32(1):23-33

eUpdate to the 2015 ESMO Guidance on CLL treatment recommendations, 27 June 2017; http://www.esmo.org/Guidelines/Haematological-Malignancies/ChronicLymphocytic-Leukemia/eUpdate-Treatment-Recommendations

Farragher TM, Lunt M, Bunn DK, Silman AJ, Symmons DPM. Early functional disability predicts both all-cause and cardiovascular mortality in people with inflammatory polyarthritis: results from the Norfolk Arthritis Register. Ann Rheum Dis 2007;66;486-492

Faurschou M, Mellemkjaer L, Sorensen IJ et al. Increased morbidity from ischemic heart disease in patients with Wegener's granulomatosis. Arthritis Rheum 2009;60:1187-1192

Faurschou M, Mellemkjaer L, Sorensen IJ. Increased morbidity from ischemic heart disease in patients with Wegener's granulomatosis. Arthritis Rheum 2009; 60:1187-1192. [10181]

Faurschou M, Sorensen IJ, Mellemkjaer L et al. Malignancies in Wegener's granulomatosis: incidence and relation to cyclophosphamide therapy in a cohort of 293 patients. J Rheumatol 2008;35:100-105.

Feldman RJ and Ahmed AR. Relevance of rituximab therapy in pemphigus vulgaris: analysis of current data and the immunologic basis for its observed responses. Expert Rev Clin Immu. 2011;7(4):529-541. [11024]

Ferlay J, Parkin DM, Steliarova-Foucher E. Estimates of cancer incidence and mortality in Europe in 2008. Eur J Cancer 2010; 462:765-781

Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. GLOBOCAN 2008 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer, 2010a. Available from: http://globocan.iarc.

Ferlay JS, Soerjomataram I, Ervik M et al. GLOBOCAN 2012 v1. 0. Cancer incidence and mortality worldwide: IARC CancerBase. 2013;11. Available from: http://globocan.iarc.fr

Fienberg, Robert. (1981). The Protracted Superficial Phenomenon in Pathergic (Wegener's) Granulomatosis. Human pathology. 12. 458-67. 10.1016/S0046-8177(81)80027-5.

Firooz A, Mazhar A, Ahmed AR. Prevalence of autoimmune diseases in the family members of patients with pemphigus vulgaris. Journal of the American Academy of Dermatology. 1994 Sep 1;31(3):434-7.

Flossmann O, Berden A, de GK, Hagen C, Harper L, Heijl C, et al. Long-term patient survival in ANCA-associated vasculitis. Ann Rheum Dis 2011 Mar;70(3):488-94.

Fujimoto S, Uezono S, Hisanaga S, Fukudome K, Kobayashi S, Suzuki K, Hashimoto H, Nakao H, Nunoi H. Incidence of ANCA-associated primary renal vasculitis in the Miyazaki Prefecture: the first population-based, retrospective, epidemiologic survey in Japan. Clin J Am Soc Nephrol. 2006 Sep;1(5):1016-22.

Furie R, Looney J, Rovin B et al. Efficacy and Safety of Rituximab in Patients with Proliferative Lupus Nephritis: Results from the Randomized, Double-Blind Phase III LUNAR Study. Poster EULAR 2010.

Furie R, Looney J, Rovin B et al. Efficacy and Safety of Rituximab in Patients with Proliferative Lupus Nephritis: Results from the Randomized, Double-blind Phase III LUNAR (LUpus Nephritis Assessment with Rituximab) Study. Presentation ACR 2009

Furst et al. Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2012. Ann Rheum Dis 2013;72:ii2-ii34.

Gabriel ES, Crowson CS, Epidemiology of, risk factors for, and possible causes of rheumatoid arthritis. UpToDate Literature review current through: Sep 2017.

Gabriel SE et al. Survival in rheumatoid arthritis. A population-based analysis of trends over 40 years. Arthritis Rheum 2003;48(1):54- 58.

Gardner-Medwin JM, Dolezalova P, Cummins C, Southwood TR. Incidence of HenochSchönlein purpura, Kawasaki disease, and rare vasculitides in children of different ethnic origins. Lancet. 2002 Oct 19;360(9341):1197-202

Garvey B. Rituximab in the treatment of autoimmune hematological disorders. Brit J Haematol 2008;141(2):149-169

Ghielmini et al, 2013. ESMO Guidelines consensus conference on malignant lymphoma 2011 part 1: diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) and chronic lymphocytic leukemia (CLL), Annals of Oncology, Volume 24, Issue 3, 1 March 2013, Pages 561–576, https://doi.org/10.1093/annonc/mds517

Giulino-Roth L. How I treat Primary Mediastinal B-cell Lymphoma. Blood 2018, 132 (8): 782-790.

Godon A, Moreau A, Talmant P, et al. Is t (14; 18)(q32; q21) a constant finding in follicular lymphoma? An interphase FISH study on 63 patients. Leukemia. 2003;17(1):255-259

Gonzalez-Gay MA et al. The epidemiology of the primary systemic vasculitides in northwest Spain: implications of the Chapel Hill Consensus Conference definitions. Arthritis & Rheumatism 2003;49(3):388-393.

Goodson NJ et al. Baseline levels of C-reactive protein and prediction of death from cardiovascular disease in patients with inflammatory polyarthritis. A ten-year followup study of a primary care-based inception cohort. Arthritis Rheum 2005;52(8):2293-2299.

Gottenberg JE, Guillevin L, Lambotte O, et al. Tolerance and short term efficacy of rituximab in 43 patients with systemic autoimmune diseases. Ann Rheum Dis 2005; 64 (6): 913-20.

Gregoriou S, Efthymiou O, Stefanaki C, et al. Management of pemphigus vulgaris: challenges and solutions. Clinical, Cosmetic and Investigational Dermatology. 2015;8:521-527. [11073]

Gribben JG. How I treat CLL up front. Blood. 2010;115(2):187-197

Grisaru S, Yuen GW, Miettunen PM, Hamiwka LA. Incidence of Wegener's granulomatosis in children. J Rheumatol. 2010 Feb;37(2):440-2. Liu X, Cui Y, Li Y, Wang C, Zhao H, Han J. Using inpatient data to estimate the prevalence of Wegener's granulomatosis in China. Intractable Rare Dis Res. 2016 Feb;5(1):31-5.

Gudowius S, Recker K, Laws HJ, et al. Identification of candidate target antigens for antibody-based immunotherapy in childhood B-cell precursor ALL. Klin Paediatr 2006;218(6):327-333.

Guillevin L, Lhote F. Polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome. Clinical aspects and treatment Rheum Dis Clin North Am 1995; 21(4):911-47.

Guillevin L, Pagnoux C, Karras A, et al. Rituximab versus azathioprine for maintenance in antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis. Accepted abstract for ACR annual meeting, 9-14 November 2012; Washington DC.

Guillevin, Loïc & Pagnoux, Christian & Karras, Alexandre & Khouatra, chahéra & Olivier, Aumaître & Cohen, Pascal & Maurier, F & Decaux, Olivier & Ninet, Jacques &Gobert, Pierre & Quémeneur, Thomas & Blanchard-Delaunay, Claire & Godmer, Pascal & Puéchal, Xavier & Carron, Pierre-Louis & Hatron, Pierre-Yves & Limal, Nicolas & Hamidou, Mohamed & Ducret, Maize & Mouthon, Luc. (2014). Rituximab versus Azathioprine for Maintenance in ANCA-Associated Vasculitis. The New England journal of medicine. 371. 1771-80. 10.1056/NEJMoa1404231.

Hahn BH, McMahon MA, Wilkinson A, et al. American College of Rheumatology Guidelines for Screening, Treatment, and Management of Lupus Nephritis. Arthritis Care & Research 2012;64(6):797-808.

Hahn-Ristic K, Rzany B, Amagai M, et al. Increased incidence of pemphigus vulgaris in southern Europeans living in Germany compared with native Germans. JEADV. 2002;16:68-71.[11025]

Hallek M and Pflug N. 2011. State of the art treatment of chronic lymphocytic Leukemia.Blood Reviews 25 (2011) 1-9.

Hallek M. Annual clinical updates in hematological malignancies: a continuing medical education series. Chronic lymphocytic leukemia: 2013 update on diagnosis, risk stratification and treatment. Am J. Hematol. 2013; 88: 804-816, 2013.

Hellmich B, Sanchez-Alamo B, Schirmer JH, et al EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update Annals of the Rheumatic Diseases Published Online First: 16 March 2023. doi: 10.1136/ard2022-223764

Herlyn K, Buckert F, Gross WL et al. Doubled prelevance rates of ANCAssocaited Vasculitides and giant cell arteritis between 1994 and 2006 in northern Germany. Rheumatology (oxford). 2014: 882-889.

Hertl M, Eming R, Veldman C. T cell control in autoimmune bullous skin disorders. J Clin Invest. 2006;116(5).1159 - 1166.[11030]

Hertl M, Jedlickova H, Karpati S, et al. Pemphigus. S2 Guideline for diagnosis and treatment – guided by the European Dermatology Forum (EDF) in cooperation with the European Academy of Dermatology and Venereology (EADV).JEADV.2015;29:405-414.[11031]

Hertl M, Jedlickova H, Karpati S,et al. Pemphigus. S2 Guideline for diagnosis and treatment – guided by the European Dermatology Forum (EDF) in cooperation with the European Academy of Dermatology and Venereology (EADV). J Eur Acad Dermatol Venereol. 2014 Oct 22.

Hoffman GS, Kerr GS, Leavitt RY, et al. Wegener granulomatosis: an analysis of 158 patients. Ann Intern Med 1992;116:488−98.

Howlader N, Noone AM, Krapcho M, Garshell J, Miller D, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A. SEER cancer statistics review, 1975-2011, national cancer institute. Bethesda, Md. 2014 Apr;86. Available from:http://seer.cancer.gov/csr/1975_2011/.

Howlader NN, Noone AM, Krapcho M et al. SEER cancer statistics review, 1975–2013. Bethesda, MD: National Cancer Institute. 2016 Apr 8;19. Available from: http://seer.cancer.gov/csr/1975_2013

Hsu DY, Brieva J, Sinha AA et al. Comorbidities and inpatient mortality for pemphigus in the USA. British Journal of Dermatology. 2016 Jun;174(6):1290-8.http://www.cancernetwork.com/cancer-management/chronic-lymphocytic-leukemia-andhairy-cell-leukemia Accessed June 2016

Hubner F, Recke A, Zillikens D, et al. Prevalence and age distribution of pemphigus and pemphigoid diseases in Germany. J Invest Dermatol. 2016;136:2495-2498. [11105]

Iaccarino L, Rampudda M, Canova M, et al. Mycophenolate mofetil: what is its place in the treatment of autoimmune rheumatic diseases? Autoimmun. Rev. 6 (2007); 190-195.

Iking-Konert C, Schmidt E, Fiehn C. Interim analysis of the retrospective German Registry (GRAID2). EULAR 2013 [THU0275].

Izarzugaza MI, Steliarova-Foucher E, Martos MC, et al. Non-Hodgkin's lymphoma incidence and survival in European children and adolescents (1978-1997): report from the Automated Childhood Cancer Information System project. Eur J Cancer 2006;42(13):2050-2063.

Jaffe ES, Harris NL, Stein H. World Health Organisation classification of tumors: pathology and genetics of tumors of haematopoietic and lymphoid tissues. Lyon: IARC Press; 2001 (available online at http://www.bluebooks.org/cgibin/who/contents?BOOK_ID=3). Reference available on request.

Jawaheer D, Seldin MF, Amos CI, et al. A genomewide screen in multiplex rheumatoid arthritis families suggests genetic overlap with other autoimmune diseases. Am J Hum Genet 2001; 68:927

Jayne D. Evidence-based treatment of systemic vasculitis. Rheumatology (Oxford). 2000 Jun;39(6):585-95.

Jeha S, Behm F, Pei D et al. Prognostic significance of CD20 expression in childhood Bcell precursor acute lymphoblastic leukemia. Blood 2006;108(10):3302-3304.

Joly P, Maho-Vaillant M, Prost-Squarcioni C. First-line rituximab combined with shortterm prednisone versus prednisone alone for the treatment of pemphigus (Ritux 3): a prospective, multicentre, parallel-group, open-label randomised trial. The Lancet. 2017 May 20;389(10083):2031-40.

Joly P, Horvath B, Patsatsi A et al. Updated S2K guidelines on the management of pemphigus vulgaris and foliaceus initiated by the european academy of dermatology and venereology (EADV). Journal of the European Academy of Dermatology and Venereology. 2020 Sep;34(9):1900-13.

Jones RB, Ferraro AJ, Chaudhry AN, Brogan P, Salama AD, Smith KG, et al. A multicenter survey of rituximab therapy for refractory antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2009 Jul;60(7):2156-68.

Kallennberg CG. Key advances in the clinical approach to ANCA-associated vasculitis. Nat Rev Rheumatol 2014;10(8):484-493.

Kamphuis S, Silverman ED. Prevalence and burden of pediatric-onset systemic lupus erythematosus. Nat Rev Rheumatol 2010; 6: 538-546.

Kanecki K, Zycinska K, Moskalewicz B, Tyszko P. Granulomatosis with polyangiitis in Poland-epidemiological study. Reumatologia. 2014 Mar 1;52(2):99

Kapetanovic MC, Lindqvist E, Geborek P, Saxne T, Eberhard K. Long-term mortality rate in rheumatoid arthritis patients with disease onset in the 1980s. Scand J Rheumatol 2011c Nov;40(6):433-8.

Kardos M, Levine D, Gürcan HM et al. Pemphigus vulgaris in pregnancy: analysis of current data on the management and outcomes. Obstet Gynecol Surv. 2009 Nov;64(11):739-49.

Kersting S, Neppelenbroek SIM, Visser HPJ, et al. Clinical practice guidelines for diagnosis and treatment of Chronic Lymphocytic Leukemia (CLL) in the Netherlands. Clin Lymphoma Myeloma Leuk 2017; S2152-2650(17):30953-9. doi: 10.1016/j.clml.2017.09.015. [Epub ahead of print]

Kim YJ, Shim JS, Choi CB, Bae SC. Mortality and incidence of malignancy in Korean patients with rheumatoid arthritis. J Rheumatol 2012 Feb;39(2):226-32.

Kishore S, Mittal V, Majithia V. Obstetric outcomes in women with rheumatoid arthritis: Results from Nationwide Inpatient Sample Database 2003-2011. Semin Arthritis Rheum. 2019 Oct;49(2):236-240.

Knight A, Askling J, Ekbom A. Cancer incidence in a population-based cohort of patients with Wegener's granulomatosis. Int J Cancer 2002;100:82−5.

Knight A, Ekbom A, Brandt L, Askling J. Increasing incidence of Wegener's granulomatosis in Sweden, 1975-2001. J Rheumatology 2006; 33(10):2060-2063.

Koldingsnes W, Nosent H. Epidemiology of ANCA associated vasculitis. Norsk Epidemiologi 2008; 18:37-48

Koldingsnes W, Nossent H. Epidemiology of Wegener's granulomatosis in northern Norway. Arthritis Rheum. 2000; 43: 2481–2487. [10175]

Koldingsnes W, Nossent H. Predictors of survival and organ damage in Wegener's granulomatosis. Rheumatology (Oxford). 2002 May;41(5):572-81.

Kuderer NM et al. Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. Cancer 2006;106(10):2258–2266

Lamanna N, Weiss MA, Dunleavy K. Chronic lymphocytic leukemia and hairy-cell leukemia.

Langan SM, Smeeth L, Hubbard R, et al. Bullous pemphigoid and pemphigus vulgarisincidence and mortality in the UK: population based cohort study. BMJ. 2008;337:1-7.[11041]

Langer-Gould A, Zhang JL, Chung J, et al. Incidence of acquired CNS demyelinating syndromes in a multiethnic cohort of children. Neurol 2011;77:1143-1148.

Lau EMC; Symmons DPM, Croft P. The epidemiology of hip osteoarthritis and rheumatoid arthritis in the Orient. Clin Orthop Relat R 1996;323:81-90.

Leshem, Y. A., Katzenelson, V., Yosipovitch, G et al. Autoimmune diseases in patients with pemphigus and their first-degree relatives. Int. J. Dermatol. 50, 827–831 (2011). [11249]

Liao KP, Alfredsson L, Karlson EW. Environmental influences on risk for rheumatoid arthritis. Curr Opin Rheumatol 2009; 21:279.

Lindhardsen J, Ahlehoff O, Gislason GH, Madsen OR, Olesen JB, Svendsen JH, et al. Risk of atrial fibrillation and stroke in rheumatoid arthritis: Danish nationwide cohort study. BMJ 2012 Mar 8;344:e1257. doi: 10.1136/bmj.e1257.:e1257.

Lopez-Olivo MA, Tayar JH, Martinez-Lopez JA et al. Risk of malignancies in patients with rheumatoid arthritis treated with biologic therapy: a meta-analysis. JAMA 2012;308:898-908.

Luqmani R, Suppiah R, Edwards CJ et al. Mortality in Wegener's granulomatosis: abiomodal pattern. Rheumatology. 2011;50:697-702.[10223]

Luqmani r, suppiah r, edwards cj, phillip r, maskell j, culliford d, et al. Mortality in wegener's granulomatosis: a bimodal pattern. Rheumatology (oxford) 2011 apr;50(4):697-702.

Ma S. Risk factors of follicular lymphoma. Expert Opinion on Medical Diagnostics. July 2012;6(4):323-333

Macintyre E, Willerford D, Morris SW. Non-Hodgkin's Lymphoma: Molecular Features of B Cell Lymphoma. Hematology Am Soc Hematol Educ Program. 2000:180-204

Mahr A et al. Prevalences of polyarteritis nodosa, microscopic polyangiitis, Wegener's granulomatosis, and Churg-Strauss syndrome in...population in 2000: a capturerecapture estimate. Arthritis & Rheumatism 2004;51(1):92-99. [10159]

Mahr A, Guillevin L, Poissonnet M, Aymé S. Prevalences of polyarteritis nodosa, microscopic polyangiitis, Wegener's granulomatosis, and Churg-Strauss syndrome in a French urban multiethnic population in 2000: a capture-recapture estimate. Arthritis & Rheumatism 2004;51(1):92-99.

Mahr A, Guillevin L, Poissonnet M, et al. Prevalences of polyarteritis nodosa, microscopic polyangiitis, Wegener's granulomatosis, and Churg-Strauss syndrome in a French urban multiethnic population in 2000: a capture-recapture estimate. Arthritis & Rheumatism 2004;51(1):92-99.

Mahr A, Guillevin L, Poissonnet M, et al. Prevalences of polyarteritis nodosa, microscopic polyangiitis, Wegener's granulomatosis, and Churg-Strauss syndrome in a French urban multiethnic population in 2000: a capture-recapture estimate. Arthritis & Rheumatism 2004;51(1):92-99. [10159].

Maggen C, Dierickx D, Cardonick E et al; International Network on Cancer Infertility Pregnancy (INCIP). Maternal and neonatal outcomes in 80 patients diagnosed with non-Hodgkin lymphoma during pregnancy: results from the International Network of Cancer, Infertility and Pregnancy. Br J Haematol. 2021 Apr;193(1):52-62.

Malleson PN, Fung MY, Rosenberg AM. The incidence of pediatric rheumatic diseases: results from the Canadian Pediatric Rheumatology Association Disease Registry. J Rheumatol 1996; 23:1981-1987.

Maradit-Kremers H, et al. Cardiovascular death in rheumatoid arthritis: a populationbased study. Arthritis Rheum, 2005;52(3):722-732

Marcos-Gragera R, Allemani C, Tereanu C et al. Survival of European patients diagnosed with lymphoid neoplasms in 2000-2002: results of the HAEMACARE project. Haematologica 2011; 96(5):720-728. [10314]

Marodi et al. Primary immunodeficiencies may reveal potential infectious diseases associated with immune-targeting treatments. J Allergy Clin lmmunol 2010; 126(5): 910-917.

Mclean-Tooke A, Aldridge C, Waugh S, et al. Methotrexate, rheumatoid arthritis and infection risk-what is the evidence? Rheumatology 2009; 48: 867-871.

Mercer LK, Green AC, Galloway JB et al. The influence of anti-TNF therapy upon incidence of keratinocyte skin cancer in patients with rheumatoid arthritis: longitudinal results from the British Society for Rheumatology Biologics Register. Ann Rheum Dis 2012;71:869-874.

Micali G, Musumeci ML and Nasca MR. Epidemiologic analysis and clinical course of 84 consecutive cases of pemphigus in eastern Sicily. Int J Dermatol. 1998;37:197-200.[11050]

Michailidou EZ, Belazi MA, Markopoulos AK, et al. Epidemiologic survey of pemphigus vulgaris with oral manifestations in northern Greece: retrospective study of 129 patients. Int J Dermatol. 2007;46:356-361.[11051]

Minard-Colin V, Brugières L, Reiter A, et al. Non-Hodgkin lymphoma in children and adolescents: progress through effective collaboration, current knowledge, and challenges ahead. J Clin Oncol 2015;33:2963□74.

Mohammad AJ et al. Prevalence of Wegener's granulomatosis, microscopic polyangiitis, polyarteritis nodosa and Churg-Strauss syndrome within a defined population in southern Sweden. Rheumatology 2007;46:1329-1337.[10163]

Morgan MD, Turnbull J, Selamet U, et al. Increased incidence of cardiovascular events in patients with antineutrophil cytoplasmic anti-body-associated vasculaites: a matched-pair cohort study. Arth Rheum 2009;60(11):3493-3500

Morgan MD, Turnbull J, Selamet U, et al. Increased incidence of cardiovascular events in patients with antineutrophil cytoplasmic antibody-associated vasculaites. Arthritis Rheum. 2009;60(11):3493-3500. [10661]

Morrison VA. Infectious complications of chronic lymphocytic Leukemia: pathogenesis, spectrum of infection, preventive approaches. Best Practice & Research Clinical Haematology 2010;23:145–153

Morrison VA. Management of infectious complications in patients with chronic lymphocytic Leukemia. Hematology 2007;1:332-338.

Morton LMH, P. Holford, T. R. Holly, E. A. Chiu, B. C. H. Vincis, P. Siagnaro, E. Willett, E. V. Franceschi, S. La Vecchia, C. Hughes, A. M. Cozen, W. Davis, S. Severson, R. K. Bernstein, L.

Mayne, S. T. Dee, F. R. Cerhan, J. R. Zheng, T. Cigarette smoking and risk of non-Hodgkin lymphoma: A pooled analysis from the International Lymphoma Epidemiology Consortium (InterLymph). Cancer Epidemiology Biomarkers and Prevention. April 2005;14(4):925-933

Morton LMW, S. S. Cozen, W. Linet, M. S. Chatterjee, N. Davis, S. Severson, R. K. Colt, J. S. Vasef, M. A. Rothman, N. Blair, A. Bernstein, L. Cross, A. J. De Roos, A. J. Engels, E. A. Hein, D. W. Hill, D. A. Kelemen, L. E. Lim, U. Lynch, C. F. Schenk, M. Wacholder, S. Ward, M. H. Zahm, S. H. Chanock, S. J. Cerhan, J. R. Hartge, P. Etiologic heterogeneity among non-Hodgkin lymphoma subtypes. Blood. 15 Dec 2008;112(13):5150-5160

Mossberg M, Segelmark M, Kahn R, Englund M, Mohammad AJ. Epidemiology of primary systemic vasculitis in children: a population-based study from southern Sweden. Scand J Rheumatol. 2018 Feb 7:1-8.

Müller AMS, Ihorst G, Mertelsmann R et al. Epidemiology of Non-Hodgkin‘s Lymphoma (NHL): Trends, Geographic Distribution, and Etiology.” Ann Hematol. 2005;84:1-12.

Murrell DF, Peña S, Joly P et al. Diagnosis and management of pemphigus: Recommendations of an international panel of experts. Journal of the American Academy of Dermatology. 2020 Mar 1;82(3):575-85.

Murray NP, Orrego S, Antonio Lopez M, Minzer S. Pregnancy in a 31-year-old woman with chronic lymphocytic leukemia: a case report and review of the literature. Hematol Transfus Cell Ther. 2021 Jul-Sep;43(3):368-370.

National Comprehensive Cancer Network (NCCN) Guidelines in B-cell Lymphomas. Version 5.2017, 26 September 2017.

National Comprehensive Cancer Network (NCCN) Guidelines in CLL. Version I.2018, 21 August 2017.

National Comprehensive Cancer Network (NCCN) Guidelines in CLL. Version Version 4. 6 January 2020.Neunert, C., Lim, W., Crowther, M., Cohen, A., Solberg, L., & Crowther, M. A.(2011). The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood, 117(16), 4190-4207. Accessed December 18, 2017. https://doi.org/10.1182/blood-2010-08-302984.

Ntatsaki E, Watts RA, Scott DGI. Epidemiology of ANCA-associated vasculitis. Rheum Dis Clin N Am. 2010;36:447-461.[11085]

AS, Cook MC. Epidemiology of primary systemic vasculitis in the Australian Capital Territory and south-eastern New South Wales. Internal Med J 2008; 38:816-823.

Onishi C, Nishikori M, Yakushijin K, et al. Lymphoma during pregnancy in Japan: a multicenter retrospective cohort study. Int J Hematol. 2022 Mar;115(3):382-90.

Paccou J and Wending D. Current treatment of psoriatic arthritis: update based on a systematic literature review to establish French Society for Rheumatology (SFR) recommendations for managing spondyloarthritis. Joint Bone Spine. 2015;82(2):80-5.

Pamuk, Ö.N., et al., The epidemiology of antineutrophil cytoplasmic antibody-associated vasculitis in northwestern Turkey. Clinical Rheumatology, 2016. 35(8): p. 2063-2071. [11250]

Panagiotakis SH, Perysinakis GS, Kritikos H, et al. The epidemiology of primarysystemic vasculitides involving small vessels in Crete (southern Greece): a comparison of older versus younger adult patients. Clinical and Experimental Rheumatology 2009; 27(3):409-415.

Pankhurst T, Savage CO, Gordon C, Harper L. Malignancy is increased in ANCAassociated vasculitis. Rheumatology (Oxford). 2004 Dec;43(12):1532-5. Epub 2004 Aug 17.

Parameswaran, A., Attwood, K., Sato, R., Seiffert-Sinha, K. & Sinha, A. A. Identification of a new disease cluster of pemphigus vulgaris with autoimmune thyroid disease, rheumatoid arthritis and type I diabetes. Br. J. Dermatol. 172, 729–738 (2015). [11251]

Pearce FA, Grainge MJ, Lanyon PC, Watts RA, Hubbard RB. The incidence, prevalence and mortality of granulomatosis with polyangiitis in the UK Clinical Practice Research Datalink. Rheumatology (Oxford). 2017 Apr 1;56(4):589-596.

Pearce, F.A., Lanyon PC, Grainge MJ et al., Incidence of ANCA-associated vasculitis in a UK mixed ethnicity population. Rheumatology, 2016. 55(9): p. 1656-1663. [11252]

Phillip R, Luqmani R. Mortality in systemic vasculitis: a systematic review. Clin Exp Rheumatol. 2008 Sep-Oct;26(5 Suppl 51):S94-104.

Pierre Charles et al 2017. Comparison of individually tailored versus fixed- schedule rituximab regimen to maintain ANCA- associated vasculitis remission: results of a multicentre, randomised controlled, phase III trial (MAINRITSAN2) [11276].

Pisanti S, Sharav Y, Kaufman E, et al. Pemphigus vulgaris: Incidence in Jews of different ethnic groups, according to age, sex, and initial lesion. Pemphigus vulgaris. 1974;38(3):382-387 [11056].

Pohl D, Hennemuth I, von KR, Hanefeld F. Pediatric multiple sclerosis and acute disseminated encephalomyelitis in Germany: results of a nationwide survey. Eur J Pediatr 2007;166:405-412.

Provan, D., Stasi, R., Newland, A. C., Blanchette, V. S., Bolton-Maggs, P., Bussel, J. B., Chong, B. H., Cines, D. B., Gernsheimer, T. B., Godeau, B., Grainger, J., Greer, I., Hunt, B. J., Imbach, P. A., Lyons, G., McMillan, R., Rodeghiero, F., Sanz, M. A., Tarantino, M., Watson, S., Young, J., & Kuter, D. J. (2010). International consensus report on the investigation and management of primary immune thrombocytopenia. Blood, 115(2), 168-186. Accessed December 19, 2017. https://doi.org/10.1182/blood-2009-06-225565.

Puechal X, Gottenberg JE, Berthelot JM, et al. Rituximab therapy for systemic vasculitis associated with rheumatoid arthritis: results from the AutoImmunity and Rituximab Registry. Arthritis Care Res 2012;64(3):331-9.

Ravandi F, O'Brien S. Immune defects in patients with chronic lymphocytic Leukemia. Cancer Immunol Immun.2006;55:197–209.

Raza K, Thambyrajah J, Townend JN, Exley AR, Hortas C, Filer A, Carruthers DM, Bacon PA. Suppression of inflammation in primary systemic vasculitis restores vascular endothelial function: lessons for atherosclerotic disease? Circulation. 2000 Sep 26;102(13):1470-2.

Reinhold-Keller E, Herlyn K, Wagner-Bastmeyer R, et al. Stable incidence of primary systemic vasculitides over five years: results from the German vasculitis register. Arthritis & Rheumatism 2005;53(1):93-99.

Reinhold-Keller E, Zeidler A, Gutfleisch J, et al. Giant cell arteritis is more prevalent in urban than rural populations: results of an epidemiological study of primary systemic vasculitidis in Germany. Rheumatology 2000;39:1396-1402.

Study MA28150 (RITAZAREM) Clinical Overview, dated November 2021.Robbins and Cotran: Pathologic Basis of Disease, 7th ed. Copyright © 2005 Saunders, An Imprint of Elsevier. (available on request)Roulland S, Lebailly P, Lecluse Y, Briand M, Pottier D, Gauduchon P. Characterization of the t(14;18) BCL2-IGH translocation in farmers occupationally exposed to pesticides. Cancer Res. Mar 15 2004;64(6):2264-2269

Sanchez AA, Acevedo EM, Sanchez CG, et al. Incidences of the primary systemic vasculitides in a Peruvian population: 233 [abstract]. J Clin Rheumatology: 2006; 12(4):75.

Sant M, Allemani C, Tereanu C et al. Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. Blood 2010 116: 3724-3734.

Shanshal M, Haddad RY. Chronic lymphocytic leukemia. Disease-a-month: DM. 2012;58(4):153-167

Simon DG, Krutchkoff D, Kaslow RA, et al. Pemphigus in Hartford county, Connecticut, from 1972 to 1977. Arch Dermatol. 1980;116:1035-1037.[11063]

Simon T, Thompson A, Gandhi K, et al. Incidence of malignancy in adult patients with rheumatoid arthritis: an updated analysis of the literature Ann Rheum Dis 2014 A.D.;73 Supp 2 [abstract]
Singh JA, Furst DE, Bharat A, et al. Update of the 2008 American College of Rheumatology Recommendations for the Use of Disease-Modifying Antirheumatic Drugs and Biologic Agents in the Treatment of Rheumatoid Arthritis. Arthritis Care Res 2012;64(5):625--639.

Smith RM, Jones RB, Guerry MJ, Laurino S, Catapano F, Chaudhry A, Smith KGC, Jayne DRW. Rituximab for remission maintenance in relapsing ANCA-associated vasculitis. Arthritis Rheum 2012; 64(11):3760-3769.

Smitten AL, Simon TA, Hochberg MC, et al. A meta-analysis of the incidence of malignancy in adult patients with rheumatoid arthritis. Arthritis Res Ther 2008b;10(2):1-8.

Solomon DH, et al. Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. Circulation. 2003;107:1303-1307.

Solomon DH, et al. Patterns of cardiovascular risk inrheumatoid arthritis. Ann Rheum Dis. 2006;65:1608-1612.

Stone JA, Merkel PA, Seo P, et al. (for the RAVE-ITN Research Group). Extended Follow-up of Treatment with Rituximab Versus Cyclophosphamide for RemissionInduction of ANCA-Associated Vasculitis: Which Subsets Are At Greatest Risk for Flare? American College of Rheumatology Meeting; Chicago. 2011:2432A. Available from: http://www.rheumatology.org/education/annual/2011_abstract.pdf. Manuscript in preparation.

Stone JH, Holbrook JT, Marriott MA, et al. Solid malignancies among patients in the Wegener's Granulomatosis Etanercept Trial. Arthritis Rheum. 2006; 54(5):1608-1618.[10179]

Suppiah R, Judge A, Batra J, et al. A model to predict cardiovascular events in patients with newly diagnosed Wegener's granulomatosis and microscopic polyangiitis. Arthris Care Res 2011;63(4):588-596.

Symmons D, Tricker K, Davis M, Dawes P, Knight, Mulherin D, Scott DL, et al. Patients with stable long-standing rheumatoid arthritis continue to deteriorate despite intensified treatment with traditional disease modifying anti-rheumatic drugs—results of the British Rheumatoid outcome study group randomized controlled clinical trial. Rheumatology 2006;45:558–565

tchal X, Gottenberg JE, Berthelot JM, et al. Rituximab therapy for systemic vasculitis associated with rheumatoid arthritis: results from the AutoImmunity and Rituximab Registry. Arthritis Care Res 2012;64(3):331-9.

Terrier B, Charles P, Aumaître O et al. ANCA-associated vasculitides: Recommendations of the French Vasculitis Study Group on the use of immunosuppressants and biotherapies for remission induction and maintenance. La Presse Médicale. 2020 Oct 1;49(3):104031.

Thierry S, Fautrel B, Lemelle I, et al. Prevalence and incidence of juvenile idiopathic arthritis: a systematic review. Joint Bone Spine 2014;81:112-117.

Thurmes P et al. Comorbid conditions and survival in unselected, newly diagnosed patients with chronic lymphocytic Leukemia. Leukemia Lymphoma 2008;49(1):49-

Tony HP, Burmester G, Schulze-KoopsH, et al. Safety and clinical outcomes of rituximab therapy in patients with different autoimmune diseases: experience from a national registry (GRAID). Arthritis Res Ther. 2011; 13(3): R75.

Turesson C, Jarenros A, Jacobsson L. Increased incidence of cardiovascular disease in patients with rheumatoid arthritis: results from a community based study. Ann Rheum Dis 2004 Aug;63(8):952-5.

Van Doornum S et al. Accelerated atherosclerosis. An extraarticular feature of rheumatoid arthritis? Arthritis Rheum 2002;46(4):862-873.

Van Spronsen DJ, Janssen-Heijnen MLG, Breed WPM, Coebergh JWW. Prevalence of co-morbidity and its relationship to treatment among unselected patients with Hodgkin's disease and non-Hodgkin's lymphoma, 1993–1996. Ann Hematol 1999;78:315–319
Van Vollenhoven RF, Emery P, Bingham CO, III, Keystone EC, Fleischmann R, Furst DE, et al. Long term safety of patients receiving rituximab in rheumatoid arthritis clinical trials. J Rheumatol 2010 Mar;37(3):558-67.

Van Vollenhoven, Emery R, Bingham P, et al, Long-term safety of rituximab: Pooled analysis of the rheumatoid arthritis global clinical trial program over 11 years [abstract]. Arthritis Rheum 2013;65(Suppl 10):2341-2342.

Verdecchia A, Francisci S, Brenner H et al. Recent cancer survival in Europe: a 2000–02 period analysis of EUROCARE-4 data. Lancet Oncol 2007 8: 784-96.

Veronique Minard-Colin, Anne Auperin, Marta Pillon, Amos Burke, James Robert Anderson, Donald A. Barkauskas. Results of the randomized Intergroup trial InterB-NHL Ritux 2010 for children and adolescents with high-risk B-cell non-Hodgkin lymphoma (B-NHL) and mature acute leukemia (B-AL): Evaluation of rituximab (R) efficacy in addition to standard LMB chemotherapy

(CT) regimen. DOI: 10.1200/JCO.2016.34.15_suppl.10507 Journal of Clinical Oncology 34, no. 15_suppl (May 2016) 10507-10507. Available from: http://ascopubs.org/doi/abs/10.1200/JCO.2016.34.15_suppl.10507#affiliationsContainer

Walton E. Giant-cell granuloma of the respiratory tract (Wegener's granulomatosis). Br Med J. 1958;2(5091):265-70.

Wang J, Wiley JM, Luddy R, Greenberg J, Feuerstein MA, Bussel JB. Chronic immune thrombocytopenic purpura in children: assessment of rituximab treatment. J Pediatr. 2005;146:217-221

Wasko MCM. Comorbid conditions in patients with rheumatoid diseases: an update. Curr Opin Rheumatol 2004;16:109-113

Watson DJ et al. All-cause mortality and vascular events among patients with rheumatoid arthritis, osteoarthritis, or no arthritis in the UK General Practice Research Database. J Rheumatol 2003;30:1196-1202

Watson L, Wyld P, Catovsky D. Disease burden of chronic lymphocytic Leukemia within the European Union. Journal compilation 2008 81:253-258.

Watts RA et al. Epidemiology of Systemic Vasculitis. A Ten-Year Study in the United Kingdom. Arthritis & Rheumatism 2000;43(2): 414-419.

Watts RA, Carruthers DM, Scott DG. Epidemiology of systemic vasculitis: changing incidence or definition? Sem Arthritis Rheum 1995;25(1):28-34.

Watts RA, Lane SE, Scott DG et al. Epidemiology of vasculitis in Europe. Ann Rheum Dis. 2001; 60: 1156–1157. [11254]

Watts RA, Mahr A, Mohammad AJ, et al. Classification, epidemiology and clinical subgrouping of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. Nephrol Dial Transplant. 2015;30:i14–i22.[11091]

Watts RA, Mooney J, Skinner J, Scott DG, Macgregor AJ. The contrasting epidemiology of granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis. Rheumatology (Oxford) 2012 May;51(5):926-31.

Watts RA, Scott DG. Epidemiology of the vasculitides. Semin Respir Crit Care Med 2004;25:455-64.Weiss PF. Pediatric vasculitis. Pediatr Clin North Am 2012;59:407-423.

Westman KW, Bygren PG, Olsson H, et al. Relapse rate, renal survival, and cancer morbidity in patients with Wegener’s granulomatosis or microscopic polyangiitis with renal involvement. J Am Soc Nephrol 1998;9:842−52.

Woldegiorgis S and Swerlick RA. Pemphigus in the southeastern United States. South Med J. 2001 Jul; 94(7):694-8. (need MRN) [11156]

Wolfe F et al. Increase in cardiovascular and cerebrovascular disease prevalence in rheumatoid arthritis. J Rheumatol 2003;30(1):36-40.

Worch J, Rohde M, Burkhardt B. Mature B-Cell Lymphoma and Leukemia in Children and Adolescents – Review of Standard Chemotherapy Regimen and Perspectives. Pediatric Hematology and Oncology 2013, 30 (6): 465-483.

Yates M, Watts RA, Bajema IM, et al EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. Annals of the Rheumatic Diseases 2016;75:1583-1594.

Young A, Koduri G, Gough A, Norton S, Dixey J, et al. Mortality in rheumatoid arthritis. Increased in the early course of disease, in ischaemic heart disease and in pulmonary fibrosis. Rheumatology 2007;46:350–357.

Zecca M, Nobili B, Ramenghi U, et al. Rituximab for the treatment of refractory autoimmune hemolytic anemia in children. Blood 2003;101(10):3857–3861.

Part VI: Summary of the risk management plan

Summary of risk management plan for Ituxredi (rituximab)

This is a summary of the RMP for Ituxredi (rituximab). The RMP details important risks of Ituxredi, how these risks can be minimised, and how more information will be obtained about Ituxredi's risks and uncertainties (missing information).

Ituxredi's summary of product characteristics (SmPC) and its package leaflet give essential information to HCPs and patients on how Ituxredi should be used.

This summary of the RMP for Ituxredi should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which will be part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Ituxredi's RMP.

I. The medicine and what it is used for

Ituxredi is intended for use in non-Hodgkin's lymphoma (NHL) (IV administration), chronic lymphocytic leukaemia (CLL) (IV administration), rheumatoid arthritis (RA), granulomatosis with polyangiitis and microscopic polyangiitis (GPA/MPA), pemphigus vulgaris (IV administration). See SmPC for the full indication. It contains rituximab as the active substance and it is given by IV administration.

Further information about the evaluation of Ituxredi's benefits can be found in Ituxredi's 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 Ituxredi, together with measures to minimise such risks and the proposed studies for learning more about Ituxredi's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Ituxredi, these measures are supplemented with *additional risk minimisation* measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed*, including PSUR assessment* so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of Ituxredi 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 Ituxredi. Potential risks are concerns for which an association with the Important risks of Ituxredi are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered.. 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 (PML)(All Indications)
Important potential risks	None
Missing information	None

II.B Summary of important risks

Important Identified Risk: Infections, Including Serious Infections (All Indications)	
Evidence for linking the risk to the medicine	The following is identified from originator product MabThera®: 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 (cut-off: 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 (cut-off: July 2012) comprising M39021, M39022, M39045, E4494. E1496, PRIMA (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 paediatric 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 minimisation 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:** *Medicine's legal status:* Medicinal product subject to restricted medical prescription **Additional risk minimization measures:** Patient Alert Card (non-oncology indications)
Additional pharmacovigilance activities	None
Important identified risk: Progressive Multifocal Leukoencephalopathy (All Indications)	
Evidence for linking the risk to the medicine	The following is identified from originator product MabThera®: MabThera SmPC DSR 1096921 Progressive Multifocal Leukoencephalopathy (PML) Cumulative update report for Rituximab, dated January 2019 (cut-off 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 (cut-off 17 November 2016)) DSR 1066994 Progressive Multifocal Leukoencephalopathy PML-Cumulative update report for Rituximab, dated 12 January 2016 (cut-off 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 (cut-off 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. **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 evaluations, 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 rituximab 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)
Additional pharmacovigilance activities	None

II.C Post-authorisation development plan

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

None.

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

None.

Part VII: Annexes

Annex 1 – EudraVigilance Interface

Available in electronic format only.

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Not applicable.

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

Not applicable.

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable.

Annex 5 - Protocols for proposed and on-going studies in RMP part IV

Not applicable.

Annex 6 - Details of proposed additional risk minimisation activities

Draft key messages of the additional risk minimisation measures

PATIENT ALERT CARD

The Patient Alert Card for Ituxredi in non-oncology indications includes the following key elements:

- The need to carry the card at all times and to show the card to all treating health care professionals
- Warning on the risk of infections and PML, including the symptoms
- The need for patients to contact their health care professional if symptoms occur

The Patient Alert Card must be agreed with the National Competent Authorities prior to distribution.

- Details of the key elements of PAC for Ituxredi in non-oncology indications:

  All patients treated with Ituxredi in non-oncology indications must always carry the PAC during each infusion that contains the information about the risks of the medicine, and instructions on when to contact their doctor if they experience symptoms. This card must be kept for 2 years after the patient's last dose of Ituxredi because the sideeffects can develop several months after treatment.

There is a potential increased risk of infections with use of Ituxredi and the possible signs of infection may include:

– Fever or cough all the time

– Weight Loss

– Pain without injury

– Feeling generally unwell or listlessness

Rarely Ituxredi can cause a serious brain infection, called PML which may result in signs such as:
– Confusion, memory loss or problems thinking

– Loss of balance or a change in the way the patient walks or talks

– Decreased strength or weakness on one side of the body

– Blurred vision or loss of vision

If a patient experiences any of the above signs, they should inform a doctor or nurse straight away and also tell them about their Ituxredi treatment.

For more details on when to seek attention from a healthcare professional and the Contact details of the Ituxredi prescriber and contact details for the patient's emergency contact, please refer to the PAC.

Annex 7 - Other supporting data (including referenced material)

Not applicable

Annex 8 – Summary of changes to the risk management plan over time

Version	Approval date Procedure	Change
0.1	Not applicable PL GB 08553/0758-59 EMEA/H/C/6224	New application
0.2	Not applicable EMEA/H/C/6224	Response to assessor's D94 comments • Acertation for additional monitoring in Part I: product overview • Annex 4: Subcutaneous route of administration removed from guided questionnaire: Off-Label Use in Paediatric Patients follow-up form and guided questionnaire: • Clarification for the distribution of PAC via MAH website • Aligned the sections mentioned by assessor to the innovator's statement.
0.3	Not applicable EMEA/H/C/6224	Response to assessor's D150 comments • Updated safety concerns to harmonize with innovator's RMP • Aligned the sections mentioned by assessor to the innovator's statement

Version	Approval date Procedure	Change
0.4	Date of approval: 19 September 2024 EMEA/H/C/6224	Removed risks related to Subcutaneous Route and all references to Subcutaneous route.
1.0	Not applicable EMEA/H/C/6224	Aligned with originator's updated RMP: • Updated the template • Updated the Part I:Product Overview • Updated the Part II:Module SII- Non clinical and SIII Clinical trial exposure. • Updated the Part II: Module SV - Post-authorisation experience. • Updated the Part II: Module SVII - Identified and potential risks . - Deleted safety concerns: 1. Hepatitis B reactivation (All indications) 2. Hypogammaglobulinaemia (Non-oncology indications) 3. Long-Term Use in GPA/MPA Patients (GPA/MPA Only) • Updated the Part II:Module SVIII-Summary of safety concern- Deleted safety concerns: 1. Hepatitis B reactivation (All indications) 2. Hypogammaglobulinaemia (Non-oncology indications) • Updated the part III Pharmacovigilance plan (including postauthorisation safety studies): III.1 Routine pharmacovigilance activities- Deleted follow-up questionnaires information III1.1 Other forms of routine pharmacovigilance activities • Updated the Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimization) V.1: Routine risk minimisation- deleted safety concerns

Version	Approval date Procedure	Change
		V.2: Additional risk minimization measures – deleted- Educational material for HCPs and patients V.3: Summary of risk minimisation measures deleted- safety concerns • Updated Part VI Summary of the risk minimisation • II.A: List of important risk and missing information and II.B Summary of important risks- Deleted safety concerns • Updated Annex 4: deleted Specific adverse event follow-up questionnaires • Updated Annex 6: Deleted educational material for HCPs and patients. 1. Progressive multifocal leukoencephalopathy 2. Ituxredi malignancy effect
1.1	Not applicable EMEA/H/C/6224	Response to EMA assessment report, to update the RMP to align it with reference product RMP Following changes made: Part II: SIV.1 - Table 2 updated to align with reference product RMP - In Table 2, Criterion for “Fertile men or women of childbearing potential not using adequate contraception (oral contraceptives, intrauterine device or barrier method of contraception in conjunction with spermicidal jelly or surgically sterile). Pregnant or breastfeeding women” is updated