Chief Medical Office & Patient Safety

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

722-0133-182-967-8-1

EU Safety Risk Management Plan

Active substance(s) (INN or common name):	Rituximab
Product(s) concerned (brand name(s)):	Rixathon® Riximyo®
Document status:	Final
Version number:	8.1
Data lock point for this RMP	16 May 2025
Date of final sign off	30 May 2025
Number of pages	83

Rationale for submitting an updated Risk Management Plan (RMP):

This RMP has been updated based on Committee for Medicinal Products for Human Use (CHMP) Type IB work sharing (WS) variation assessment report for procedure EMA/VR/0000249103 dated 24 Apr 2025. To align with innovator MabThera RMP v.25.1, removed information for important potential risk "administration route error [Non-Hodgkin's lymphoma (NHL)/ Chronic lymphocytic leukemia (CLL)]" and associated health care professional (HCP) alert card.

Summary of significant changes in this RMP:

Part	Major changes compared to RMP v.8.0
Part I	As per new information in SmPC, updated the information in 'pharmacotherapeutics group', 'Information about its composition', 'Indication' and 'Dosage'.
Part II: SVII	Removed important potential risk "administration route error (NHL/CLL)".
Part II: SVIII	Removed important potential risk "administration route error (NHL/CLL)" from summary of safety concerns.
Part III	None
Part IV	None
Part V	Removed information for important potential risk "administration route error (NHL/CLL)" and HCP alert card.
Part VI	Updated in line with the changes to Part II and Part V.
Part VII	Updated in line with the changes to above parts.

Other RMP versions under evaluation

No RMP versions are currently under evaluation.

Details of the currently approved RMP:

Version number: 7.1

Approved with procedure(s): EMEA/H/C/003903/IB/0051; EMEA/H/C/004729/IB/0052

Date of approval (opinion date): 27-Feb-2023

QPPV name: Dr. Mohamed Ali Kotal

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorization holder's QPPV. Electronic signatures are available on file.

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List of abbreviations

ACR	American College of Rheumatology
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
ANCA	Antineutrophil cytoplasmic antibody
AST	Aspartate aminotransferase
BAL	Burkitt leukemia (mature B-cell acute leukemia)
BL	Burkitt lymphoma
BLL	Burkitt-like lymphoma
CD4, CD8	Cluster of Differentiation 4 or 8: co-receptors of T cell receptors on T cells assisting in immune response
CDC	Complement-Dependent Cytotoxicity
CHMP	Committee for Medicinal Products for Human Use
CHOP	Cyclophosphamide, doxorubicin, vincristine, prednisolone
CI	Confidence interval
CLL	Chronic lymphocytic leukemia
CMV	Cytomegalovirus
CNS	Central nervous system
CTCAE	Common Terminology Criteria for Adverse Events
CVP	Cyclophosphamide, vincristine, prednisone
DDD	Defined daily dose
DLBCL	Diffuse large B-cell lymphoma
DMARD	Disease-modifying antirheumatic drug
EPAR	European Public Assessment Report
FL	Follicular lymphoma
FU	Follow-up
GPA	Granulomatosis with polyangiitis
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCP	Health Care Professional
HIV	Human immunodeficiency virus
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IV	Intravenous
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
MAH	Marketing Authorization Holder
MDRD	Modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities

MPA	Microscopic polyangiitis
MRI	Magnetic Resonance Imaging
MTX	Methotrexate
NA	Not applicable
NHL	Non-Hodgkin's lymphoma
NYHA	New York Heart Association
PD	Pharmacodynamics
PL	Package leaflet
PK	Pharmacokinetics
PML	Progressive multifocal leukoencephalopathy
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PT	Preferred Term
PV	Pemphigus vulgaris
RA	Rheumatoid arthritis
RMP	Risk Management Plan
ROW	Rest of World
SmPC	Summary of Product Characteristics
TNF	Tumor necrosis factor
ULN	Upper limit of normal
URTI	Upper respiratory tract infection
WS	Work Sharing

1 Part I: Product(s) Overview

Table 1-1 Part I.1 - Product Overview

Active substance(s) (INN or common name)	Rituximab
Pharmacotherapeutic group(s) (ATC Code)	Antineoplastic agents, monoclonal antibodies and antibody drug conjugates. (L01FA01)
Marketing Authorization Holder	Sandoz GmbH
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Rixathon® Riximyo® (internal code name used throughout the document: GP2013)
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: GP2013 (INN: Rituximab) is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B-lymphocytes. The antibody is an IgG, kappa immunoglobulin containing murine light- and heavy-chain variable region sequences and human constant region sequences. GP2013 is composed of two heavy chains of 451 amino acids and two light chains of 213 amino acids (based on cDNA analysis) and has an approximate molecular weight of 145 kDa. GP2013 has a binding affinity for the CD20 antigen of approximately 5 nM.
	Summary of mode of action: Rituximab has several elements that can contribute to its mode of action, which are considered the same in all indications, namely the depletion of B cells. While the Fab domain of rituximab binds to the CD20 antigen on B-lymphocytes, 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 natural killer cells. Moreover, binding of rituximab to the CD20 antigen on B-lymphocytes has also been demonstrated to activate signalling cascades that result in the induction of cell death via apoptosis.
	Important information about its composition: The chimeric anti-CD20 antibody is produced by mammalian cell (Chinese Hamster Ovary) suspension culture. The anti-CD20 antibody is purified by affinity and ion exchange chromatography. This medicinal product contains 2.3 mmol (or 52.6 mg) sodium per 10 mL vial and 11.5 mmol (or 263.2 mg) sodium per 50 mL vial, equivalent to 2.6% (for 10 ml mL vial) and 13.2% (for 50 ml mL vial) of the WHO recommended maximum daily intake of 2 g sodium for an adult.

	This medicinal product contains 7.0 mg of polysorbate 80 (E 433) per 10 mL vial and 35.0 mg of polysorbate 80 (E 433) per 50 mL vial, which is equivalent to 0.7 mg/mL. Polysorbates may cause allergic reactions.
Hyperlink to the Product Information	[Current approved SmPC]
Indication(s) in the EEA	Current (if applicable): **Non-Hodgkin's lymphoma (NHL)** Rixathon/Riximyo is indicated for the treatment of previously untreated adult patients with stage III-IV follicular lymphoma in combination with chemotherapy. Rixathon/Riximyo maintenance therapy is indicated for the treatment of adult follicular lymphoma patients responding to induction therapy. Rixathon/Riximyo 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. Rixathon/Riximyo is indicated for the treatment of adult patients with CD20 positive diffuse large B-cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy. Rixathon/Riximyo in combination with chemotherapy is indicated for the treatment of paediatric patients (aged 6 months to less than 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)** Rixathon/Riximyo in combination with chemotherapy is indicated for the treatment of adult patients with previously untreated and relapsed/refractory chronic lymphocytic leukaemia. Only limited data are available on efficacy and safety for patients previously treated with monoclonal antibodies including rituximab or patients refractory to previous rituximab plus chemotherapy. **Rheumatoid arthritis** Rixathon/Riximyo in combination with methotrexate is indicated for the treatment of adult patients with severe active rheumatoid arthritis 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** Rixathon/Riximyo, 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).

	Rixathon/Riximyo, in combination with glucocorticoids, is indicated for the induction of remission in paediatric patients (aged 2 to less than 18 years old) with severe, active GPA (Wegener's) and MPA. **Pemphigus vulgaris** Rixathon/Riximyo is indicated for the treatment of adult patients with moderate to severe pemphigus vulgaris (PV).
	Proposed (if applicable): Not applicable
Dosage in the EEA	Current (if applicable): **Non-Hodgkin's lymphoma** **Follicular non-Hodgkin's lymphoma** *Combination therapy* The recommended dose of Rixathon/Riximyo in combination with chemotherapy for induction treatment of previously untreated or relapsed/ refractory patients with follicular lymphoma is: 375 mg/m^2 body surface area per cycle, for up to 8 cycles. Rixathon/Riximyo should be administered on day 1 of each chemotherapy cycle, after intravenous administration of the glucocorticoid component of the chemotherapy if applicable. *Maintenance therapy* • Previously untreated follicular lymphoma The recommended dose of Rixathon/Riximyo used as a maintenance treatment for patients with previously untreated follicular lymphoma who have responded to induction treatment is: 375 mg/m^2 body surface area once every 2 months (starting 2 months after the last dose of induction therapy) until disease progression or for a maximum period of two years (12 infusions in total). • Relapsed/refractory follicular lymphoma The recommended dose of Rixathon/Riximyo used as a maintenance treatment for patients with relapsed/refractory follicular lymphoma who have responded to induction treatment is: 375 mg/m^2 body surface area once every 3 months (starting 3 months after the last dose of induction therapy) until disease progression or for a maximum period of two years (8 infusions in total). *Monotherapy* • Relapsed/refractory follicular lymphoma The recommended dose of Rixathon/Riximyo monotherapy used as induction treatment for adult patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy is: 375 mg/m^2 body surface area, administered as an intravenous infusion once weekly for four weeks. For retreatment with Rixathon/Riximyo monotherapy for patients who have responded to previous treatment with rituximab monotherapy for relapsed/refractory follicular lymphoma, the recommended dose is: 375 mg/m^2 body surface area, administered as an intravenous infusion once weekly for four weeks.

	Adult diffuse large B-cell non- Hodgkin's lymphoma Rixathon/Riximyo should be used in combination with CHOP chemotherapy. The recommended dosage is 375 mg/m^2 body surface area, administered on day 1 of each chemotherapy cycle for 8 cycles after intravenous infusion of the glucocorticoid component of CHOP. Safety and efficacy of rituximab have not been established in combination with other chemotherapies in diffuse large B cell non-Hodgkin's lymphoma. **Chronic lymphocytic leukaemia** The recommended dosage of Rixathon/Riximyo in combination with chemotherapy for previously untreated and relapsed/refractory patients is 375 mg/m^2 body surface area administered on day 0 of the first treatment cycle followed by 500 mg/m^2 body surface area administered on day 1 of each subsequent cycle for 6 cycles in total. The chemotherapy should be given after Rixathon/Riximyo infusion. For marketing authorizations with indication Rheumatoid arthritis only: **Rheumatoid arthritis** Patients treated with Rixathon/Riximyo must be given the patient alert card with each infusion. A course of Rixathon consists of two 1,000 mg intravenous infusions. The recommended dosage of Rixathon is 1,000 mg by intravenous infusion followed by a second 1,000 mg intravenous 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. Available data suggest that clinical response is usually achieved within 16 to 24 weeks of an initial treatment course. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within this time period. **Granulomatosis with polyangiitis and microscopic polyangiitis** Patients treated with Rixathon/Riximyo must be given the patient alert card with each infusion. *Adult induction of remission* The recommended dosage of Rixathon/Riximyo for induction of remission therapy in adult patients with GPA and MPA is 375 mg/m^2 body surface area, administered as an intravenous infusion once weekly for 4 weeks (four infusions in total). *Adult maintenance treatment* Following induction of remission with Rixathon/Riximyo, 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, Rixathon/Riximyo maintenance treatment should be initiated during the 4-week period that follows disease remission.

Rixathon/Riximyo 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 Rixathon/Riximyo 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 Rixathon/Riximyo maintenance therapy, up to 5 years.

Pemphigus vulgaris

Patients treated with Rixathon/Riximyo must be given the patient alert card with each infusion.

The recommended dosage of Rixathon/Riximyo for the treatment of pemphigus vulgaris 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 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.

Special populations

Paediatric population

Non-Hodgkin's lymphoma

In paediatric patients from 6 months to less than 18 years of age with previously untreated, advanced stage CD20 positive DLBCL/BL/BAL/BLL, Rixathon/Riximyo should be used in combination with systemic Lymphome Malin B (LMB) chemotherapy. The recommended dosage of Rixathon/Riximyo is 375mg/m^2 BSA, administered as an IV infusion. No Rixathon/Riximyo dose adjustments, other than by BSA, are required.

The safety and efficacy of rituximab paediatric patients aged 6 months to less than 18 years of age has not been established in indications other than previously untreated advanced stage CD20 positive DLBCL/BL/BAL/BLL. Only limited data are available for patients under 3 years of age.

Rixathon/Riximyo should not be used in paediatric patients from birth to 6 months of age with CD20 positive diffuse large B-cell lymphoma.

Table 1 Posology of rituximab administration for Non-Hodgkin's lymphoma paediatric patients

Cycle	Day of treatment	Administration details
Prephase (COP)	No rituximab given	-

Induction course 1 (COPDAM1)	Day -2 (corresponding to day 6 of the prephase) 1st rituximab infusion	During the 1st induction course, prednisone is given as part of the chemotherapy course, and should be administered prior to rituximab.
	Day 1 2nd rituximab infusion	Rixathon/Riximyo will be given 48 hours after the first infusion of rituximab.
Induction course 2 (COPDAM2)	Day -2 3rd rituximab infusion	In the 2nd induction course, prednisone is not given at the time of rituximab administration.
	Day 1 4th rituximab infusion	Rituximab will be given 48 hours after the third infusion of rituximab.
Consolidation course 1 (CYM/CYVE)	Day 1 5th rituximab infusion	Prednisone is not given at the time of rituximab administration.
Consolidation course 2 (CYM/CYVE)	Day 1 6th rituximab infusion	Prednisone is not given at the time of rituximab administration.
Maintenance course 1 (M1)	Day 25 to 28 of consolidation course 2 (CYVE) No rituximab given	Starts when peripheral counts have recovered from consolidation course 2 (CYVE) with ANC> 1.0 x 10^9/l and platelets > 100 x 10^9/l
Maintenance course 2 (M2)	Day 28 of maintenance course 1 (M1) No rituximab given	-
ANC = Absolute Neutrophil Count; COP = Cyclophosphamide, Vincristine, Prednisone; COPDAM = Cyclophosphamide, Vincristine, Prednisolone, Doxorubicin, Methotrexate; CYM = CYtarabine (Aracytine, Ara-C), Methotrexate; CYVE = CYtarabine (Aracytine, Ara-C), VEposide (VP16)		

Table 2 Treatment Plan for Non-Hodgkin's lymphoma paediatric patients: Concomitant Chemotherapy with rituximab

Treatment Plan	Patient Staging	Administration details
Group B	Stage III with high LDH level (> N x 2), Stage IV CNS negative	Prephase followed by 4 courses: 2 induction courses (COPADM) with HDMTX 3g/m² and 2 consolidation courses (CYM)
Group C	Group C1: B- AL CNS negative, Stage IV & BAL CNS positive and CSF negative	Prephase followed by 6 courses: 2 induction courses (COPADM) with HDMTX 8g/m², 2 consolidation courses (CYVE) and 2 maintenance courses (M1 and M2)
	Group C3: BAL CSF positive, Stage IV CSF positive	

	Consecutive courses should be given as soon as blood count recovery and patient's condition allows BAL = Burkitt leukaemia (mature B-cell acute leukaemia); CSF = Cerebrospinal Fluid; CNS = Central Nervous System; HDMTX = High-dose Methotrexate; LDH = Lactic Acid Dehydrogenase *Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA)* *Induction of remission* The recommended dosage of Rixathon/Riximyo for induction of remission therapy in paediatric patients with severe, active GPA or MPA is 375 mg/m^2 BSA, administered as an IV infusion once weekly for 4 weeks. The safety and efficacy of Rixathon/Riximyo in paediatric patients (aged 2 to less than 18 years of age) has not been established in indications other than severe, active GPA or MPA. Rixathon/Riximyo should not be used in paediatric patients less than 2 years of age with severe, active GPA or MPA as there is a possibility of an inadequate immune response towards childhood vaccinations against common, vaccine preventable childhood diseases (e.g. measles, mumps, rubella, and poliomyelitis). Elderly No dose adjustment is required in patients aged 65 years and above. *Method of administration* All indications Rixathon/Riximyo is for intravenous use. The prepared Rixathon/Riximyo solution should be administered as an intravenous infusion through a dedicated line. It should not be administered as an intravenous push or bolus.
	Proposed (if applicable): Not applicable
Pharmaceutical form(s) and strengths	Current (if applicable): GP2013 is a concentrate for solution for infusion. Each vial contains either 100 mg or 500 mg, in 10 mL or 50 mL, respectively (concentration: 10 mg/mL).
	Proposed (if applicable): not applicable
Is/will the product be subject to additional monitoring in the EU?	No

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

A single-dose pharmacokinetics (PK)/pharmacodynamics (PD) study and a 4-week repeat-dose toxicity study (with PK and PD assessments), both in non-human primates, indicated comparable exposure to GP2013 and MabThera® (the registered trademark sign will be omitted for better readability throughout the section). These studies also showed comparable B-cell depletion at different doses of GP2013 and MabThera (as the pharmacological effect of rituximab); all dose levels showed slow but complete recovery (to approximate pre-dose values) by the end of the observation period.

In the comparative 4-week repeated dose toxicity study, with subsequent 6 months recovery phase, comparable results in both treatment groups were seen: e.g. no unscheduled deaths, no clinical findings regarding behavior and appearance, feces, or injection site, no differences in body weight developments were observed. All hematology and chemistry parameters obtained were comparable between the two groups. Germinal centers of follicles were lacking with varying incidences in the lymphatic organs examined (mesenteric lymph nodes, spleen, mandibular lymph node, axillary lymph node) in all groups. It was occasionally accompanied by minimal to slight lymphoid depletion of spleen or axillary lymph node in single animals. These changes were considered to represent the morphological correlate of the reduced B cell number in peripheral blood and regarded as pharmacological effect of the test substances. At the microscopic level, minimal to moderate foamy histiocytes were observed at interim kill in one animal in the GP2013, and two animals in the MabThera 100 mg/kg dose treated groups. These observations had not been previously reported from MabThera toxicity studies. Since this change is very rare as background finding, a relationship to treatment cannot be completely excluded. Importantly, they were not seen in the recovery group animals, suggesting a transient pharmacological effect. All other histopathological observations at interim as well as final necropsy were consistent with the expected spectrum of background pathology in cynomolgus monkeys. There were no unusual macroscopic findings suggestive of target organ toxicity.

Further safety information was drawn from a human tissue cross-reactivity study - no unexpected off target binding was observed with GP2013.

In summary, GP2013 was well tolerated, no unexpected safety signals were observed, and the overall safety profile was comparable to that of MabThera.

Table 2-1 Key safety findings from non-clinical studies and relevance to human usage: toxicity and safety findings

Key Safety findings (from non-clinical studies)	Relevance to human usage
Toxicity: • Comparable results in both treatment groups (GP2013 vs. MabThera) in a comparative 4-week repeated dose toxicity study in cynomolgus monkey: no unscheduled deaths, no clinical findings regarding behavior and appearance, feces, or injection site, no differences in body weight developments	Not relevant
Other toxicity-related information or data • No unexpected off target binding with GP2013 in a human tissue cross-reactivity study	Not relevant

Overall, no new risks or potential risks were identified during the non-clinical development of GP2013. PK, PD and toxicity studies conducted with GP2013, together with the established knowledge available for the reference product, demonstrate that the non-clinical safety profile of GP2013 is comparable to that of MabThera. Important identified and potential risks reported on the reference product MabThera will be addressed by the Sandoz pharmacovigilance program on GP2013.

3 Part II Safety specification Module SIII Clinical trial exposure

3.1 Part II Module SIII Clinical trial exposure

The clinical development program consisted of four clinical studies, which provide safety data for GP2013:

- Study GP13-101: Phase I trial to assess the safety and pharmacokinetics of GP2013 monotherapy administered weekly in Japanese patients with CD20 positive low tumor burden indolent B cell Non-Hodgkin's Lymphoma.
  The study was conducted as requested by PMDA to assess safety and PK of GP2013 monotherapy administered in 6 Japanese patients with CD20+ low tumor burden indolent NHL using the weekly dosing regimen in accordance with the approved label of Rituxan in Japan (Zenyaku Kogyo Co., Ltd. (2014)).
- Study GP13-201: A randomized, double-blind, controlled study to evaluate pharmacokinetics, pharmacodynamics, safety and efficacy of GP2013 and rituximab in patients with rheumatoid arthritis refractory or intolerant to standard DMARDs and one or up to three anti-TNF therapies.
  The study consisted of two parts. In Part I, GP2013 was compared with MabThera, and in Part II with US-licensed Rituxan. In the exposure tables below, exposure to GP2013 in Part I and Part II was pooled.
- Study GP13-301: A randomized, controlled, double-blind Phase III trial to compare the efficacy, safety and pharmacokinetics of GP2013 plus cyclophosphamide, vincristine, prednisone vs. MabThera® plus cyclophosphamide, vincristine, prednisone, followed by GP2013 or MabThera® maintenance therapy in patients with previously untreated, advanced stage follicular lymphoma.
- Study GP13-302: A randomized, double-blind, controlled, parallel-group, multicenter study to assess the safety and immunogenicity of transitioning to GP2013 or re-treatment with Rituxan® or MabThera® in patients with active rheumatoid arthritis, previously treated with Rituxan® or MabThera®.

Exposure to GP2013 in the four studies (GP13-101, GP13-201 (Part I and Part II), GP13-301, and GP13-302) is summarized in the following tables.

Table 3-1 Clinical trial exposure

Indication	Clinical trial	Number of patients exposed to GP2013
Low grade CD20+ NHL	GP13-101	6
Rheumatoid arthritis	GP13-201 (Part I and Part II)	133
Follicular lymphoma	GP13-301	312
Rheumatoid arthritis	GP13-302	53

NHL=non-Hodgkin's lymphoma

Table 3-2 Duration of trial exposure per indication: Rheumatoid arthritis (GP13-201 Part I and Part II, GP13-302; 1000 mg)

Duration of Trial Exposure (at least)	Number of patients	Patients years* (Total/Mean/Median/Range)
12 months	75	86.27/1.150/1.095/1.00 - 1.54
Total	186	155.97/0.839/0.997/0.01 - 1.54

*Patient years for each patient = (date of last contact – first dose of investigational drug +1)/365.25

Table 3-3 Duration of trial exposure per indication: Low grade NHL and follicular lymphoma (GP2013-101, GP2013-301; 375 mg/m^2)

Duration of Trial Exposure (at least)	Number of patients	Patients years* (Total/Mean/Median/Range)
12 months	242	632.02/2.612/2.931/1.00 - 4.04
Total	318	673.51/2.118/2.682/0.10 - 4.04

NHL=non-Hodgkin's lymphoma
*Patient years for each patient = (date of last contact – first dose of investigational drug +1)/365.25

Table 3-4 Duration of trial exposure per indication (by age group and gender): Rheumatoid arthritis (GP13-201 Part I and Part II, GP13-302; 1000 mg)

	Patients			Patients years* (Total/Mean/Median/Range)		
Age groups (years)	M	F	Total	M	F	Total
18-<45	8	23	31	7.37/0.922/1.076/0.32 - 1.37	21.00/0.913/0.999/0.10 - 1.32	28.37/0.915/0.999/0.10 - 1.37
45-<65	14	104	118	11.47/0.819/0.991/0.43 - 1.34	84.19/0.809/0.995/0.04 - 1.54	95.65/0.811/0.995/0.04 - 1.54
≥65	7	30	37	5.87/0.839/0.851/0.43 - 1.31	26.08/0.869/0.997/0.01 - 1.44	31.95/0.864/0.997/0.01 - 1.44
Total	29	157	186	24.71/0.852/0.986/0.32 - 1.37	131.26/0.836/0.999/0.01 - 1.54	155.97/0.839/0.997/0.01 - 1.54

*Patient years for each patient = (date of last contact – first dose of investigational drug +1)/365.25
M=male; F=female

Table 3-5 Duration of trial exposure per indication (by age group and gender): Low grade NHL and follicular lymphoma (GP13-101, GP13-301; 375 mg/m^2)

	Patients			Patients years* (Total/Mean/Median/Range)		
Age groups (years)	M	F	Total	M	F	Total
<60	70	95	165	135.46/1.935/2.393/0.13 - 3.18	203.67/2.144/2.806/0.10 - 4.04	339.12/2.055/2.631/0.10 - 4.04
≥60	63	90	153	127.94/2.031/2.648/0.19 - 3.11	206.45/2.294/2.879/0.22 - 4.02	334.39/2.186/2.694/0.19 - 4.02
Total	133	185	318	263.39/1.980/2.502/0.13 - 3.18	410.12/2.217/2.861/0.10 - 4.04	673.51/2.118/2.682/0.10 - 4.04

	Patients			Patients years* (Total/Mean/Median/Range)		
Age groups (years)	M	F	Total	M	F	Total

NHL=non-Hodgkin's lymphoma
*Patient years for each patient = (date of last contact – first dose of investigational drug +1)/365.25
M=male; F=female

Table 3-6 Duration of trial exposure per indication (by number of infusions): Rheumatoid arthritis (GP13-201 Part I and Part II, GP13-302; 1000 mg)

Number of Infusions	Number of patients	Patients years* (Total/Mean/Median/Range)
1	5	0.29/0.058/0.041/0.01 - 0.17
2	88	52.95/0.602/0.480/0.09 - 1.48
4	93	102.73/1.105/1.038/0.56 - 1.54
Total	186	155.97/0.839/0.997/0.01 - 1.54

*Patient years for each patient = (date of last contact – first dose of investigational drug +1)/365.25

Table 3-7 Duration of trial exposure per indication (by number of infusions): Low grade NHL and follicular lymphoma (GP2013-101, GP2013-301; 375 mg/m^2)

Number of Infusions	Number of patients	Patients years* (Total/Mean/Median/Range)
1	6	1.94/0.324/0.197/0.10 - 1.03
2	6	4.80/0.800/0.278/0.14 - 3.00
3	5	1.38/0.276/0.326/0.15 - 0.36
4	4	1.17/0.292/0.292/0.19 - 0.39
5	4	2.35/0.587/0.397/0.28 - 1.27
6	5	3.20/0.641/0.550/0.40 - 0.98
7	2	1.24/0.621/0.621/0.42 - 0.82
8	32	21.48/0.671/0.513/0.22 - 2.96
9	16	16.28/1.017/0.891/0.72 - 2.95
10	22	30.05/1.366/1.118/0.97 - 3.00
11	7	9.87/1.410/1.405/1.29 - 1.55
12	11	17.22/1.566/1.572/1.38 - 1.71
13	5	10.41/2.083/1.919/1.87 - 2.77
14	9	18.13/2.014/1.977/1.90 - 2.27
15	4	11.41/2.853/2.982/2.40 - 3.05
16	171	495.36/2.897/2.960/2.32 - 4.02
17	1	3.03/3.031/3.031/3.03 - 3.03
20	8	24.18/3.023/2.945/2.65 - 4.04
Total	318	673.51/2.118/2.682/0.10 - 4.04

NHL=non-Hodgkin's lymphoma
*Patient years for each patient = (date of last contact – first dose of investigational drug +1)/365.25

Table 3-8 Duration of trial exposure per indication (by race and gender): Rheumatoid arthritis (GP13-201 Part I and Part II, GP13-302; 1000 mg)

	Patients			Patient years* (Total/Mean/Median/Range)		
Race	**M**	**F**	**Total**	**M**	**F**	**Total**
Asian	3	10	13	3.68/1.227/1.246/1.19 - 1.25	8.77/0.877/1.018/0.09 - 1.54	12.45/0.957/1.188/0.09 - 1.54
Black	0	1	1		1.00/1.002/1.002/1.00 - 1.00	1.00/1.002/1.002/1.00 - 1.00
Caucasian	26	142	168	21.03/0.809/0.908/0.32 - 1.37	118.49/0.834/0.997/0.01 - 1.48	139.52/0.830/0.997/0.01 - 1.48
Native American	0	1	1		0.44/0.444/0.444/0.44 - 0.44	0.44/0.444/0.444/0.44 - 0.44
Pacific Islander	0	1	1		0.46/0.463/0.463/0.46 - 0.46	0.46/0.463/0.463/0.46 - 0.46
Other	0	2	2		2.10/1.049/1.049/1.00 - 1.10	2.10/1.049/1.049/1.00 - 1.10
Total	29	157	186	24.71/0.852/0.986/0.32 - 1.37	131.26/0.836/0.999/0.01 - 1.54	131.26/0.836/0.999/0.01 - 1.54

*Patient years for each patient = (date of last contact – first dose of investigational drug +1)/365.25
M=male; F=female

Table 3-9 Duration of trial exposure per indication (by race and gender): Low grade NHL and follicular lymphoma (GP2013-101, GP2013-301; 375 mg/m^2)

	Patients			Patient years* (Total/Mean/Median/Range)		
Race	**M**	**F**	**Total**	**M**	**F**	**Total**
Caucasian	80	134	214	172.32/2.154/2.682/0.14 - 3.18	317.54/2.370/2.921/0.16 - 4.04	489.86/2.289/2.901/0.14 - 4.04
Black	5	1	6	7.30/1.460/1.021/0.52 - 2.97	2.88/2.877/2.877/2.88 - 2.88	10.18/1.697/1.499/0.52 - 2.97
Asian	41	36	77	64.57/1.575/1.377/0.13 - 3.01	55.76/1.549/1.266/0.10 - 3.00	120.33/1.563/1.268/0.10 - 3.01
Native American	0	2	2		6.00/3.002/3.002/2.96 - 3.05	6.00/3.002/3.002/2.96 - 3.05
Other	7	12	19	19.20/2.743/2.960/1.87 - 3.02	27.94/2.329/2.910/0.39 - 3.44	47.14/2.481/2.960/0.39 - 3.44
Total	133	185	318	263.39/1.980/2.502/0.13 - 3.18	410.12/2.217/2.861/0.10 - 4.04	673.51/2.118/2.682/0.10 - 4.04

NHL=non-Hodgkin's lymphoma
*Patient years for each patient = (date of last contact – first dose of investigational drug +1)/365.25
M=male; F=female

4 Part II Safety specification Module SIV: Populations not studied in clinical trials

Since this MAA has been submitted for a similar biological medicinal product under Article 10 (4) of Directive 2001/83/EC, as amended, a tailored clinical program was justified. Rheumatoid arthritis and NHL are considered sensitive indications that can be used to detect differences

between treatments. Therefore, four studies were conducted in these populations, the MabThera and/or Rituxan controlled studies GP13-201 and GP13-302 in patients with rheumatoid arthritis (RA) and two studies, one-arm study GP13-101 in Japanese patients with low grade NHL and the confirmatory efficacy and safety study GP13-301 in patients with follicular lymphoma (FL). The design, conduct, PK characteristics of GP2013 and MabThera/Rituxan, were generally similar to those characteristics in historical clinical studies. Therefore, the totality of available information supports the assay sensitivity of the four studies. Other patient populations were not studied in GP2013 development program.

4.1 Part II SIV.1. Exclusion criteria in pivotal clinical studies within the development program

In general, the majority of exclusion criteria were in line with the SmPC MabThera or aimed at minimization of bias and confounding of study results. For clinical study GP13-301, the contraindications and precautions of the label of the chemotherapy backbone cyclophosphamide, vincristine, prednisone (CVP) were also taken into account.

Table 4-1 Important exclusion criteria in pivotal studies in the development program

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Hypersensitivity to the active substance or any of the study drug ingredients	Hypersensitivity to rituximab is rare. Patients with hypersensitivity should not be treated with Rixathon / Riximyo.	No	Hypersensitivity is listed as a contraindication in section 4.3 of the Rixathon / Riximyo SmPC. In section 4.4 of the Rixathon / Riximyo SmPC, adequate warning and advice are given how to use Rixathon / Riximyo in patients with hypersensitivity reactions. Hypersensitivity is listed as a common adverse drug reaction in section 4.8 of the Rixathon / Riximyo SmPC.
Active, severe infections	Serious infections, including fatalities, can occur during therapy with rituximab. Rixathon / Riximyo should not be administered to patients with an active, severe infection (e.g. tuberculosis, sepsis	No	Active, severe infections are listed as a contraindication in section 4.3 of the Rixathon / Riximyo SmPC.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
	and opportunistic infections). Patients with severe, active infections should not be treated with Rixathon / Riximyo. Physicians should exercise caution when considering the use of Rixathon / Riximyo in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection.		
Patients in a severely immunocompromised state	Serious infections, including fatalities, can occur during therapy with rituximab. Patients in a severely immunocompromised state should not be treated with Rixathon / Riximyo. Physicians should exercise caution when considering the use of Rixathon / Riximyo in patients with a history of recurring or chronic infections or with underlying conditions that may further predispose patients to serious infection.	No	Patients in a severely immunocompromised state are included in section 4.3 Contraindications of the Rixathon / Riximyo SmPC.
Severe heart failure (New York Heart Association Class IV) or severe, uncontrolled cardiac disease	Angina pectoris, cardiac arrhythmias such as atrial flutter and fibrillation, heart failure and/or myocardial infarction have occurred in patients treated with rituximab. Therefore,	No	Severe heart failure (New York Heart Association Class IV) or severe, uncontrolled cardiac disease is listed as a contraindication in section 4.3 of the Rixathon / Riximyo SmPC.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
	patients with a history of cardiac disease should be monitored closely.		
Female patient who is nursing, pregnant or planning pregnancy within 12 months after the last infusion after the last study drug	Lack of data for safe use during breastfeeding and pregnancy	Yes	Missing information on use in pregnancy and lactation is mentioned in sections 4.6 Fertility, pregnancy and lactation and 5.3 Preclinical safety data of the Rixathon / Riximyo SmPC.
Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, UNLESS they are using a highly effective method of birth control	Lack of data for safe use during breastfeeding and pregnancy	Yes	Missing information on use in pregnancy and lactation is mentioned in sections 4.6 Fertility, pregnancy and lactation and 5.3 Preclinical safety data of the Rixathon / Riximyo SmPC.
GP13-101			
Received radiotherapy within last 28 days prior to administration, or not recovered from previous radiotherapy	Avoiding confounding or bias of safety or efficacy data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only
Received immunotherapy, chemotherapy, antibodies and experimental treatment within last 28 days prior to administration, or not recovered from previous treatment	Avoiding confounding or bias of safety or efficacy data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only
Received monoclonal antibody therapy other than rituximab as prior line of therapy	Avoiding confounding or bias of safety data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only
Had not responded to rituximab therapy previously	To follow standard of care	No	Not related to safety concerns of Rixathon / Riximyo, used to exclude patients for who further

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
			treatment with rituximab would not have been standard of care
Clinical evidence of central nervous system involvement by lymphoma or any evidence of spinal cord compression by lymphoma	Avoiding confounding or bias of safety data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only
Evidence of uncontrolled, acute or chronic infections (except active severe infections)	Broader range of infections was excluded as necessary by contraindications to avoid confounding or bias of safety data	No	Infections which are not severe are expected to be controlled by appropriate clinical measures
Receiving chronic or high dose of systemic corticosteroids	Avoiding confounding or bias of safety or efficacy data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only
Other malignancies within 5 years prior to date of screening, with the exception of adequately treated *in situ* carcinoma of the cervix uteri, basal or squamous cell carcinoma or non-melanomatous skin cancer	Avoiding confounding or bias of safety data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only
Concurrent serious illnesses, uncontrolled medical conditions, or other medical history including clinically relevant abnormal laboratory values, which in the investigator's opinion would interfere with patient's participation in the study, or with the interpretation of study results	Avoiding confounding or bias of safety data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
GP13-201			
RA patients with functional status class IV classified according to the ACR 1991 revised criteria.	Avoiding confounding or bias of safety and efficacy data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only
Patients with levels of serum IgG, IgM and IgA below LLN at Visit 1 and/or Visit 2.	Avoiding confounding or bias of safety data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only
Patients with systemic manifestations of RA, with the exception of Sjögren's syndrome.	Avoiding confounding or bias of safety or efficacy data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only
Patients taking high potency opioid analgesics	Avoiding confounding or bias of safety or efficacy data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only
Female patients nursing (lactating / breast-feeding), pregnant or planning of pregnancy within 12 months after the last infusion of study drug, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (cut-off as defined by the central laboratory)	Lack of data for safe use during breastfeeding and pregnancy	Yes	Missing information on use in pregnancy and lactation is mentioned in sections 4.6 Fertility, pregnancy and lactation and 5.3 Preclinical safety data of the Rixathon / Riximyo SmPC.
Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, UNLESS they are using a highly effective method of birth control (i.e. one that	Lack of data for safe use during breastfeeding and pregnancy	Yes	Missing information on use in pregnancy and lactation is mentioned in sections 4.6 Fertility, pregnancy and lactation and 5.3 Preclinical safety data of the Rixathon / Riximyo SmPC.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
results in a less than 1% per year failure rate when used consistently and correctly, such as implants, injectables, combined oral contraceptives and intrauterine devices). Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) is not acceptable.			
Patients who have had any therapy with intra-articular injections (e. g. corticoid) required by a flare up to 4 weeks before randomization	Avoiding confounding or bias of safety or efficacy data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only
Patients with underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, infectious or gastrointestinal conditions, which, in the opinion of the investigator, immunocompromises the patient and/or places the patient at unacceptable risk by receiving immunomodulatory therapy within the study – especially patients with clinical history of Felty's Syndrome.	Avoiding confounding or bias of safety data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only
Patients with significant medical problems, including but not limited to the	Angina pectoris, cardiac arrhythmias such as atrial flutter and fibrillation, heart	No	Severe heart failure (New York Heart Association Class IV) or severe, uncontrolled cardiac disease is listed as a

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
following: uncontrolled hypertension (≥ 160/95 mmHg), congestive heart failure (New York Heart Association (NYHA) status of class III or IV).	failure and/or myocardial infarction have occurred in patients treated with rituximab. Therefore, patients with a history of cardiac disease should be monitored closely.		contraindication in section 4.3 of the Rixathon / Riximyo SmPC.
	With respect to other than NYHA class IV heart failure - avoiding confounding or bias of safety data.		Other than NYHA class IV heart failure conditions not related to safety concerns of Rixathon / Riximyo, used for trial optimization only
Patients with total WBC count < 3000/µL, platelets < 100,000/µL, neutrophils < 1,500/µL or hemoglobin < 8.5 g/dL (85 g/L) at Visit 1 and/or Visit 2.	Avoiding confounding or bias of safety or efficacy data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only
History of clinically significant liver disease or liver injury as indicated by abnormal liver function tests such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), or alkaline phosphatase. Any single parameter may not exceed 3 x upper limit of normal (ULN). A single parameter elevated up to and including 3 x ULN should be re-checked once more as soon as possible, and in all cases, at least prior to randomization	Avoiding confounding or bias of safety data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Patients with history of renal trauma, glomerulonephritis, a single kidney or a calculated Glomerular Filtration Rate (calculated as per 4-variable MDRD-formula) < 60 mL/min/1.73 square meter	Avoiding confounding or bias of safety data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only
History of lymphoproliferative disease or any known malignancy or history of malignancy within the past 5 years prior to randomization (except non-melanoma skin cancer which has been treated with no evidence of recurrence in the past 3 months, carcinoma in situ of the cervix, polyps (removed) in the colon with non-invasive malignancy)	Avoiding confounding or bias of safety data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only
Patients with any medical, neurologic or psychiatric condition, which in the investigator's opinion would preclude the patient from completing all protocol requirements	Avoiding confounding or bias of safety or efficacy data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only
Patients with a history or evidence of ongoing drug or alcohol abuse within the last 6 months before randomization	Avoiding confounding or bias of safety or efficacy data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only
Patients who have lost or donated ≥400 mL blood in the 8	Avoiding confounding or bias of safety data	No	Not related to safety concerns of Rixathon /

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
weeks prior to randomization			Riximyo, used for trial optimization only
Inability or unwillingness to undergo repeated venipuncture (poor tolerability or lack of access to veins)	Practical study conduct considerations	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only
Patients with plans to receive live vaccines during the study or within 4 weeks prior to randomization	Avoiding confounding or bias of safety data	No	As per SmPC MabThera, "vaccination with live virus vaccines is not recommended whilst on MabThera or whilst peripherally B cell depleted."
Known infection with HIV according to patient history. [(For Argentina only) Infection with HIV at screening]	Avoiding confounding or bias of safety data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only
Active or latent hepatitis B (HBsAg positive) or hepatitis C at screening	Patients with active hepatitis B disease should not be treated with Rixathon. For hepatitis C- safety concern on potential disease exacerbation	No	In Sections 4.4 of the SmPC, adequate warning and advice are given about the use of Rixathon / Riximyo in patients with positive hepatitis B serology (either HBsAg or HBcAb). Such patients should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation. Patients with active hepatitis B disease should not be treated with Rixathon. Reactivation of Hepatitis B in patients with RA is listed as a very rare adverse drug reaction in section 4.8 of the Rixathon / Riximyo SmPC. For active Hepatitis C - active, severe infections are listed as a contraindication in

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
			section 4.3 of the Rixathon / Riximyo SmPC.
Patients with other inflammatory diseases which might confound the evaluation of the efficacy (e.g. Crohn's disease, ulcerative colitis)	Avoiding confounding or bias of efficacy data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only
Patients with ongoing, chronic infectious disease or history of recurrent infectious diseases and with a history of active tuberculosis within the previous 2 years should not be included. Patients with evidence of tuberculosis infection as defined by either a positive PPD skin test or a positive QuantiFERON TB-Gold test may enter the study if further work-up establishes conclusively that the patient has no evidence of active tuberculosis	Avoiding confounding or bias of safety data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only
Active systemic infections during the two weeks (exception: common cold) prior to randomization.	Avoiding confounding or bias of safety data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only
Recent arthroplasty (within 3 months prior to randomization)	Avoiding confounding or bias of safety or efficacy data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only
Patients with a current severe progressive or uncontrolled disease which in the judgment of the clinical	Avoiding confounding or bias of safety or efficacy data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
investigator renders the patient unsuitable for the study			
History of allergy (medication history) to any of the compounds used in the study	Avoiding confounding or bias of safety or efficacy data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only
Scheduled surgery during the study treatment period	Avoiding confounding or bias of safety or efficacy data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only
Concurrent therapy with any other investigational medicinal product within 30 days or 5 times the half-life, whichever is longer, prior to randomization	Avoiding confounding or bias of safety or efficacy data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only
GP13-301			
Grade 3b (aggressive) FL or any histology other than FL Grade 1, 2 or 3a.	Clear definition of trial indication	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only
Histological evidence of transformation to high grade or diffuse large B-cell lymphoma	Clear definition of trial indication	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only
Previously received any prior therapy for lymphoma (except involved field radiation 4 weeks prior to first administration of up to 2 lesions)	Clear definition of trial indication (untreated patients)	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only
Evidence of significant leukemic disease	Clear definition of trial indication	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only
Clinical evidence of central nervous system involvement by lymphoma or any evidence of spinal	Avoiding confounding or bias of safety data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
cord compression by lymphoma			
Evidence of uncontrolled, active infections (except active severe infections)	Broader range of infections was excluded as necessary by contraindications to avoid confounding or bias of safety data	No	SmPC: Warnings and precautions: Infections: Withhold rituximab and institute appropriate anti-infective. Section 1.5: Rituximab products are not recommended for use in patients with severe, active infections.
Receiving chronic or high dose of systemic corticosteroids	Avoiding confounding or bias of safety or efficacy data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only
Other malignancies within 5 years prior to date of screening, with the exception of adequately treated in situ carcinoma of the cervix uteri, basal or squamous cell carcinoma or non-melanomatous skin cancer	Avoiding confounding or bias of safety data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only
Concurrent serious illnesses, uncontrolled medical conditions, or other medical history including clinically relevant abnormal laboratory values, which in the investigator's opinion would interfere with patient's participation in the study, or with the interpretation of study results	Avoiding confounding or bias of safety data Including contraindications to vincristine and cyclophosphamide	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only
Major surgery, open biopsy or trauma within 4 weeks prior to date of screening, or need for major surgery during the	Avoiding confounding or bias of safety data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
course of the study treatment expected			
Female patient who is nursing, pregnant or planning pregnancy within 12 months after the last infusion after the last study drug	Lack of data for safe use during breastfeeding and pregnancy.	Yes	Missing information on use in pregnancy and lactation is mentioned in sections 4.6 Fertility, pregnancy and lactation and 5.3 Preclinical safety data of the Rixathon / Riximyo SmPC.
Therapy with any other investigational medicinal product within the last 30 days or 5 times the half-life, whichever is longer	Avoiding confounding or bias of safety or efficacy data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only
Planning to receive live vaccines during the study or has received life vaccines 4 weeks prior to date of screening	Not recommended during treatment with Rixathon / Riximyo	No	As per SmPC MabThera, “vaccination with live virus vaccines is not recommended whilst on MabThera or whilst peripherally B cell depleted.”
Use of growth factors or transfusion to meet study eligibility requirements during screening period	Avoiding confounding or bias of safety data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only
GP13-302			
RA of functional status class IV classified according to the ACR 1991 revised criteria.	Avoiding confounding or bias of safety data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only
Systemic manifestation of RA, with the exception of Sjögren’s syndrome	Avoiding confounding or bias of safety data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only
Use of any other investigational drugs within 30 days prior to screening (or within 5 half-lives or until the expected PD effect has returned to baseline, whichever is longer)	Avoiding confounding or bias of safety data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Requiring treatment with any biological medicinal product during the study other than the study medication	Avoiding confounding or bias of safety data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only
Treatment with any biologics for any indication since the start of last treatment with either US-licensed Rituxan or EU-approved MabThera	Avoiding confounding or bias of safety data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only
History of severe hypersensitivity to either Rituxan or MabThera or any of its excipients, requiring drug discontinuation	Avoiding confounding or bias of safety data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only
Therapy with any DMARDs (including tofacitinib) other than methotrexate (MTX) or combination of MTX with hydroxychloroquine or MTX with chloroquine or MTX with sulfasalazine within 4 weeks prior to randomization. In case of leflunomide it has to be discontinued 8 weeks prior to randomization (if a cholestyramine washout is performed, leflunomide has to be discontinued 4 weeks prior to randomization)	Avoiding confounding or bias of safety data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only
Previous treatment with any cell depleting therapies, including investigational agents (e.g. anti-CD52, anti-	Avoiding confounding or bias of safety data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
CD4 (Cluster of Differentiation 4), anti-CD5, anti-CD3, anti-CD19, anti-CD11a, anti-CD22, BLys/ BAFF, and other than rituximab anti-CD20 agents)			
Current treatment or need for treatment with any prohibited medications (as defined by the Protocol)	Avoiding confounding or bias of safety data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only
Any serious illness or uncontrolled medical condition, including but not limited to severe infections, significant hepatic or renal disease, uncontrolled hypertension (defined as ≥160/95mmHg), congestive heart failure (NYHA class III or IV), or other severe, uncontrolled cardiac disease.	Serious infections, including fatalities, can occur during therapy with rituximab. Rixathon / Riximyo should not be administered to patients with an active, severe infection (e.g. tuberculosis, sepsis and opportunistic infections). Patients with severe, active infections should not be treated with Rixathon / Riximyo. Physicians should exercise caution when considering the use of Rixathon / Riximyo in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection. Angina pectoris, cardiac arrhythmias such as atrial flutter and fibrillation, heart	No	Active, severe infections are listed as a contraindication in section 4.3 of the Rixathon / Riximyo SmPC. Severe heart failure (New York Heart Association Class IV) or severe, uncontrolled cardiac disease is listed as a contraindication in section 4.3 of the Rixathon / Riximyo SmPC. Other than NYHA class IV heart failure conditions not related to safety concerns of Rixathon / Riximyo, used for trial optimization only

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
	failure and/or myocardial infarction have occurred in patients treated with rituximab. Therefore, patients with a history of cardiac disease should be monitored closely. With respect to conditions other than severe reactions Avoiding confounding or bias of safety data		
Any medical condition, which in the investigator's opinion, would preclude the patient from completing all protocol requirements.	Avoiding confounding or bias of safety data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only
Any of the following laboratory values at screening: WBC < 3,000/µL; Platelets < 100,000/µL; Neutrophils < 1,500/µL; Hemoglobin < 85 g/L; AST > 3 × ULN (upper limit of normal); ALT > 3 × ULN; gamma-glutamyl transferase (GGT) > 3 × ULN; alkaline phosphatase (AP) > 3 × ULN; estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 (eGFR calculated as per 4-variable MDRD formula); immunoglobulin G (IgG) and/or IgM and/or IgA below LLN	Avoiding confounding or bias of safety data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Positive serology to hepatitis C infection (i.e. positive antibody against Hepatitis C virus)	Avoiding confounding or bias of safety data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only
Positive serology to hepatitis B infection (i.e. positive HBsAg)	Patients with active hepatitis B disease should not be treated with Rixathon.	No	In Sections 4.4 of the SmPC, adequate warning and advice are given that patients with active hepatitis B disease should not be treated with Rixathon. Reactivation of Hepatitis B in patients with RA is listed as a very rare adverse drug reaction in section 4.8 of the Rixathon / Riximyo SmPC.
In case a patient is HBsAg negative but positive for hepatitis B core antibody [anti-HBc], this patient can only be included after consultation with a hepatitis expert to clarify the potential risk of hepatitis B reactivation, required hepatitis B monitoring and antiviral therapy	Such patients should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation.	No	In Sections 4.4 of the SmPC, adequate warning and advice are given about the use of Rixathon / Riximyo in patients with positive hepatitis B serology (either HBsAg or HBcAb). Such patients should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation. Reactivation of Hepatitis B in patients with RA is listed as a very rare adverse drug reaction in section 4.8 of the Rixathon / Riximyo SmPC.
History of serious recurrent or chronic infectious disease (excluding fungal infections of the nail beds) or active systemic infection within 2 weeks prior to screening or during the screening period, except for common cold	Serious infections, including fatalities, can occur during therapy with rituximab. Patients with a severely immunocompromised state should not be treated with Rixathon / Riximyo. Physicians should exercise caution when	No	Active, severe infections are listed as a contraindication in section 4.3 of the Rixathon / Riximyo SmPC.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
	considering the use of Rixathon / Riximyo in patients with a history of recurring or chronic infections or with underlying conditions, which may further predispose patients to serious infection.		
Severely immunocompromised state, including but not limited to Felty's syndrome and known HIV infection	Serious infections, including fatalities, can occur during therapy with rituximab. Patients with a severely immunocompromised state should not be treated with Rixathon / Riximyo. Physicians should exercise caution when considering the use of Rixathon / Riximyo in patients with a history of recurring or chronic infections or with underlying conditions, which may further predispose patients to serious infection.	No	Patients in a severely immunocompromised state are included in section 4.3 Contraindications of the Rixathon / Riximyo SmPC.
Any malignancy prior to screening, with exception of adequately treated *in situ* carcinoma of the cervix uteri, basal or squamous cell carcinoma or non-melanomatous skin cancer, or non-invasive malign colon polyps that have been removed with no evidence of recurrence	Avoiding confounding or bias of safety data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only
Active tuberculosis. If a QuantiFERON®-	Avoiding confounding or bias of safety data	No	Not related to safety concerns of Rixathon /

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Tuberculosis (TB) Gold test at screening is positive, further work-up, according to local guidelines/practices needs to be performed to conclusively establish that that the patient has no evidence of active tuberculosis			Riximyo, used for trial optimization only
Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive serum hCG laboratory test (> 5 mIU/mL)	Lack of data for safe use during breastfeeding and pregnancy	Yes	Missing information on use in pregnancy and lactation is mentioned in sections 4.6 Fertility, pregnancy and lactation and 5.3 Preclinical safety data of the Rixathon / Riximyo SmPC.
Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, UNLESS they agree to use highly effective methods of contraception during the study and up to 12 months after the last infusion of study medication. Women are considered not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms)	Lack of data for safe use during breastfeeding and pregnancy	Yes	Missing information on use in pregnancy and lactation is mentioned in sections 4.6 Fertility, pregnancy and lactation and 5.3 Preclinical safety data of the Rixathon / Riximyo SmPC.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential			
History of vaccination with live vaccines within 4 weeks prior to randomization or known to require live vaccines during the 6 month period after the randomization visit	Avoiding confounding or bias of safety data	No	As per SmPC MabThera, "vaccination with live virus vaccines is not recommended whilst on MabThera or whilst peripherally B cell depleted."
History or evidence of ongoing drug or alcohol abuse within the last 6 months before screening	Avoiding confounding or bias of safety data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only
Blood donation or blood loss of >400 mL in the 8 weeks prior to randomization	Avoiding confounding or bias of safety data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only
Inability or unwillingness to undergo repeated venipuncture (poor tolerability or lack of access to veins)	Avoiding confounding or bias of safety data	No	Not related to safety concerns of Rixathon / Riximyo, used for trial optimization only

4.2 Part II Module SIV.2. Limitations to detect adverse reactions in clinical trial development programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, or adverse reactions with a long latency.

Clinical trial experience with GP2013 comprises 186 patients with RA and a follow-up time of up to 1.5 years, and 318 patients with low grade FL, with a follow-up time of up to 3 years. This experience (circa 720 patient-years) limits the ability to detect rare and very rare events.

However, since GP2013 showed a similar PK, PD, and safety profile to that of reference rituximab in non-clinical studies and a similar PK and safety profile in the clinical trials, it is justified to build also on the extensive clinical trial experience that has accumulated for the reference rituximab, as described above.

Children

There is no clinical trial experience with GP2013 in children.

In line with the Paediatric Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use, GP2013, as similar biological medicinal product, is exempted from the requirement to submit a Paediatric Investigational Plan (PIP).

Based on the information available in the RMP v25.1 for MabThera, the safety profile of rituximab in paediatric patients (aged ≥ 6 months to < 18 years old) with previously untreated advanced stage CD20 positive DLBCL/BL/BAL/BLL was generally consistent in type, nature and severity with the known safety profile in adult NHL and CLL patients. When rituximab is used for the induction of remission in paediatric patients (aged ≥ 2 to < 18 years old) with severe, active GPA (Wegener's granulomatosis) and MPA, the safety profile of rituximab in paediatric GPA or MPA patients was consistent in type, nature, and severity with the known safety profile in adult patients in the approved autoimmune indications, including adult GPA or MPA (SmPC MabThera).

As the safety profiles of GP2013 and MabThera are similar, the same can be assumed for GP2013.

Elderly

Clinical trial experience in elderly is limited and no pharmacological data had been generated for this sub-population. In study GP13-201 Part I, 20 patients with RA aged ≥65 years were exposed to GP2013. In study GP13-101, 1 patient with FL and in study GP13-301, 149 patients with FL aged ≥60 years were exposed to GP2013. However, according to the information available for reference rituximab no dose adjustment is required in elderly (SmPC MabThera). As the PK properties of GP2013 and MabThera are similar, the same can be assumed for GP2013.

Based on the information available for the reference rituximab, the incidence of Grade 3/4 adverse drug reaction (ADR) was similar between elderly (≥65 years) and younger patients (<65 years) for monotherapy rituximab used in oncological indications. When rituximab is used in combination for the treatment of previously untreated or relapsed/refractory CLL, the incidence of Grade 3/4 blood and lymphatic AEs was higher in elderly patients than in younger patients (SmPC MabThera). As the safety profiles of GP2013 and MabThera are similar, the same can be assumed for GP2013.

Based on the information available for the reference rituximab, exploratory analyses of the benefit of maintenance treatment showed a less pronounced effect in patients >70 years of age; however, sample sizes were small. As the efficacy of GP2013 and MabThera are similar, the same can be assumed for GP2013.

Across all development studies in RA, the treatment benefit was similar in patients independent of age.

- Use in different age ranges: No special precautions for different age ranges ≥18 years
- Need for laboratory screening prior to use: No specific requirements
- Effect of multiple co-existing impairments: No specific information available
- ADRs of special concern: No specific ADR of special concern in elderly
- Effect of multiple medications: No dose adjustment recommended

Pregnant or breast feeding women

No clinical trial experience with GP2013 in pregnant or breast-feeding woman is available.

B-cell levels in human neonates following maternal exposure to rituximab have not been studied in clinical trials for MabThera. 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. Similar effects have been observed in animal studies. For these reasons, rituximab should not be administered to pregnant women unless the possible benefit outweighs the potential risk (SmPC MabThera).

Based on the information provided for MabThera and 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 Rixathon / Riximyo.

- Number of pregnancies and outcomes: No pregnancy in a patient exposed to GP2013 was reported in the clinical trials.
- Analysis of why contraceptive measures failed: not applicable
- Implications for use under less controlled conditions: Cases of transient B-cell depletion and lymphocytopenia have been reported in some infants born to mothers exposed to MabThera (SmPC MabThera).

Patients with hepatic impairment

Patients with clinically significant liver disease or liver injury (as indicated by abnormal liver function tests such as AST, ALT, or alkaline phosphatase) were excluded from studies GP13-101, GP13-201, GP13-301 and GP13-302.

Based on the information available for the reference rituximab, no PK data are available in patients with hepatic impairment (SmPC MabThera).

Patients with renal impairment

Patients with a history of renal trauma, glomerulonephritis, a single kidney or a calculated Glomerular Filtration Rate (GFR) (calculated as per 4-variable modification of diet in renal disease (MDRD)-formula) of <60 mL/min/1.73m^2 were excluded from study GP13-201, while patients with significant renal disease were excluded from study GP13-302. In studies GP13-101 in low grade NHL and GP13-301 in FL, serum creatinine level had to be <2 × ULN or <2.5 × ULN, respectively, or, in both studies, the calculated creatinine clearance had to be >50 mL/min at screening.

Based on the information available for the reference rituximab, no PK data are available in patients with renal impairment (SmPC MabThera).

Patients with other relevant co-morbidity

- Cardiovascular

RA patients with severe heart failure (NYHA class IV), or severe, uncontrolled cardiovascular disease were excluded from studies GP13-201 and GP13-302. Patients with adequate cardiac function (cardiac ejection fraction ≥45%) without clinically significant abnormalities were included in studies GP13-101 and GP13-301.

The use of rituximab is contraindicated in such patients due to concern for cardiac complications of infusion reactions.

Patients with a disease severity different from the inclusion criteria in the clinical trial population

Patients with RA with functional status class IV classified according to the American College of Rheumatology (ACR) 1991 revised criteria were excluded from studies GP13-201 and GP13-302.

According to the SmPC MabThera, the treatment benefit was similar in RA, independent of disease status, across all development studies.

Patients with FL with WHO histological grade 3b were excluded from study GP13-301. These FL cases have more in common with diffuse large B cell lymphoma (DLBCL) and are treated with rituximab in combination with chemotherapy backbones that are more aggressive than CVP, which was used in study GP13-301.

Sub-populations carrying known and relevant polymorphisms

Even if there are studies showing an association between genetic polymorphism of the FCGR3A allele and response to rituximab therapy in RA, NHL, and CLL (Mellor et al 2013; Tarnowski et al 2016), the majority of these findings are still inconclusive and inconsistent.

According to the SmPC MabThera, no specific testing for any pharmacogenetics marker is recommended.

Patients of different racial and/or ethnic origin

Patients of various races and ethnic origin have been included in studies with GP2013. The low number of non-Caucasians in clinical studies with GP2013 did however not allow for a statistical relevant conclusion regarding any potential difference. According to the SmPC MabThera, the treatment benefit was similar in RA, independent of race, across all development studies with MabThera. Data on implications of race and ethnicity in patients with NHL and CLL on the efficacy and safety of rituximab could not be identified.

4.3 Part II Module SIV.3. Limitations in respect to populations typically underrepresented in clinical trial development programs

Table 4-2 Exposure of special populations included or not in clinical trial development programs

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 hepatic impairment	Patients with clinically significant liver disease or liver injury (as indicated by abnormal liver function tests such as AST, ALT, or alkaline phosphatase) were not included in the clinical development program.
• Patients with renal impairment	RA patients with a history of renal trauma, glomerulonephritis, a single kidney or a calculated Glomerular Filtration Rate of <60 mL/min/1.73m^2 were excluded from study GP13-201. RA patients with significant renal disease were excluded from study GP13-302. In studies GP13-101 in low grade NHL and GP13-301 in FL, serum creatinine level had to be <2 × ULN or <2.5 × ULN, respectively, or, in both studies, the calculated creatinine clearance had to be >50 mL/min at screening.
• Patients with cardiovascular impairment	RA patients with severe heart failure (NYHA class IV), or severe, uncontrolled cardiovascular disease were excluded from studies GP13-201 and GP13-302. Patients with adequate cardiac function (cardiac ejection fraction ≥45%) without clinically significant abnormalities were included in studies GP13-101 and GP13-301.
• Immunocompromised patients	Severely immunocompromised patients were not included in the clinical development program
• Patients with a disease severity different from inclusion criteria in clinical trials	Patients with RA with functional status class IV classified according to the ACR 1991 revised

Type of special population	Exposure
	criteria were not included in the clinical development program. Patients with FL with WHO histological grade 3b were not included in the clinical development program.
Population with relevant different ethnic origin	Patients of various races and ethnic origin have been 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
• Elderly	37 patients with RA aged ≥65 years and 153 patients with FL aged ≥60 years were exposed to GP2013.

Table 4-3 Exposure of special populations included or not in clinical trial development programs (programmed part) (GP13-201 Part I and Part II, GP13-302; 1000mg)

	GP2013 N=186		Rituxan/MabThera N=233	
Special population	**Subjects n (%)**	**Patient years***	**Subjects n (%)**	**Patient years***
Age <65	149 (80.1)	124.02	180 (77.3)	157.15
Age ≥65	37 (19.9)	31.95	53 (22.7)	45.54
Total	186 (100.0)	155.97	233 (100.0)	202.69

*Patient years for each patient = (date of last contact – first dose of investigational drug +1)/365.25. Patient years is based on the number of patients in each category.

Table 4-4 Exposure of special populations included or not in clinical trial development programs (programmed part) (GP13-101, GP13-301; 375mg/m^2)

	GP2013 N=318		MabThera N=315	
Special population	**Subjects n (%)**	**Patient years***	**Subjects n (%)**	**Patient years***
Age <60	165 (51.9)	339.12	175 (55.6)	403.66
Age ≥60	153 (48.1)	334.39	140 (44.4)	316.27
Total	318 (100.0)	673.51	315 (100.0)	719.92

*Patient years for each patient = (date of last contact – first dose of investigational drug +1)/365.25. Patient years is based on the number of patients in each category.

5 Part II Safety specification Module SV: Post-authorization experience

5.1 Part II Module SV.1. Post-authorization exposure

5.1.1 Part II Module SV.1.1 Method used to calculate exposure

An estimate of the patient exposure is generally calculated by dividing the worldwide sales volume of active pharmaceutical ingredient sold by the defined daily dose (DDD). However, no DDDs have been established for rituximab because the dosing and schedule is based on indication; and dosing is intermittent not daily. Therefore, the exposure to rituximab from marketing experience is considered by Sandoz to be most appropriately expressed as individual patient doses, rather than an estimate of patient-treatment-years. The calculation is based upon an assumption that all patients received the maximal dose recommended based on the mg/m^2 body surface area dosing i.e. 1 g dose per patient.

$$\text{Patient exposure (patient doses)} = \frac{\text{Quantity of rituximab sold (g)}}{\text{Maximum recommended dose (g/patient)}}$$

5.1.2 Part II Module SV.1.2. Exposure

The estimated exposure is provided in Table 5-1.

Table 5-1 Cumulative exposure from marketing experience - Estimated exposure (patient doses)*

	EEA	Canada	Japan	ROW	Total
Parenteral (100 mg vials)	130,338	3,669	91,521	171,518	397,046
Parenteral (500 mg vials)	1,590,659	49,858	409,196	842,052	2,891,765
Overall	1,720,997	53,527	500,717	1,013,570	3,288,811

EEA: European Economic Area; ROW: Rest of World (Includes Great Britain)

This table includes cumulative data obtained until 31-Oct-2024.

Source of data: worldwide sales volume

* The calculations using the formula for usage of Patient Exposure (Patient Dosage) was changed for accuracy of calculation results. Hence, current sales data figures are different than previous reports.

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

6.1 Potential for misuse for illegal purposes

Not applicable; a potential for abuse and dependence is not anticipated based on the mechanism of action of rituximab.

7 Part II Safety specification Module SVII: Identified and potential risks

7.1 Part II SVII.1. Identification of safety concerns in the initial RMP submission

This section is not applicable; the RMP was already approved.

7.2 Part II SVII.2: New safety concerns and reclassification with a submission of an updated RMP

This section has been updated to be aligned to the safety concerns provided in reference product MabThera RMP v.25.1. As per the guidance provided in PRAC PSUR assessment report for Procedure EMEA/H/C/PSUSA/00002652/202311 dated 30 May 2024, MAH is obliged to align the safety concerns with the latest safety profile of reference product (MabThera RMP v.25.1).

The important identified risks 'Hepatitis B (HBV) reactivation (all indications)', 'Hypogammaglobulinemia (non-oncology indications)', important potential risk 'Administration route error (NHL/CLL) and missing information 'Long-term use in GPA/MPA patients (GPA/MPA)' was removed from the list of safety concerns.

There were no safety concerns associated with the 90-minute infusion regimen, neither in study CGP2013ES01R nor in the literature, for second and subsequent infusions of rituximab in patients with NHL or CLL who did not experience a Grade 3 or 4 infusion-related reaction with their first infusion.

7.3 Part II SVII.3: Details of important identified risks, important potential risks, and missing information

7.3.1 SVII.3.1. Presentation of important identified risks and important potential risks

All Indications: Important Identified Risk: Infections (including serious infections):

Table 7-1 NHL/CLL: Clinical trial data of infections (including serious infections)

	GP2013 N=318 n (%) 95% CI	MabThera N=315 n (%) 95% CI	GP2013 vs. MabThera Risk Difference 95% CI
Number of subjects with at least one TEAE	179 (56.3) (50.8, 61.7)	179 (56.8) (51.4, 62.3)	-0.536 (-8.259, 7.187)
Maximum severity			
Grade 1 AEs	33 (10.4)	34 (10.8)	
Grade 2 AEs	108 (34.0)	111 (35.2)	
Grade 3 AEs	28 (8.8)	29 (9.2)	
Grade 4 AEs	10 (3.1)	5 (1.6)	

	GP2013 N=318 n (%) 95% CI	MabThera N=315 n (%) 95% CI	GP2013 vs. MabThera Risk Difference 95% CI
Serious TEAEs	30 (9.4)	31 (9.8)	
Leading to death	3 (0.9)	1 (0.3)	

TEAE: Treatment-emergent adverse event
Numbers (n) represent counts of subjects.
Infections were defined using adverse events listed in the SOC Infections and infestation, excluding infestations.
Note: Pooled data from GP2013-101 and GP2013-301.
MedDRA version: 17.0 for GP2013-101 and 20.0 for GP2013-301, CTCAE version 4.03

Table 7-2 RA: Clinical trial data of infections (including serious infections)

	GP2013 N=186 n (%) 95% CI	Rituxan/MabThera N=233 n (%) 95% CI	GP2013 vs Rituxan/MabThera Risk Difference 95% CI
Number of subjects with at least one event	51 (27.4) (21.0, 33.8)	78 (33.5) (27.4, 39.5)	-6.057 (-14.878, 2.764)
Maximum severity			
Mild	30 (16.1)	45 (19.3)	
Moderate	17 (9.1)	30 (12.9)	
Severe	4 (2.2)	3 (1.3)	
SAEs	5 (2.7)	6 (2.6)	
AE outcome			
Recovered/resolved	47 (25.3)	73 (31.3)	
Recovering/resolving	4 (2.2)	5 (2.1)	
Not recovered/not resolved	4 (2.2)	7 (3.0)	
Recovered/resolved with sequelae	1 (0.5)	0	
Fatal	0	1 (0.4)	
Unknown	0	0	
Leading to death	0	1 (0.4)	

Infections were defined using adverse events listed in SOC infections and infestations, excluding infestations.
Numbers (n) represent counts of subjects.
Note: Pooled data from GP13-201 and GP13-302.
Treatment emergent AE presented only.
MedDRA version 19.1 for GP13-201 and 19.0 for GP13-302.

Table 7-3 All indications: Important identified risk infections (including serious infections): Other details

Infections (including serious infections)	Details System Organ Class (SOC): Infections and infestations
Potential mechanisms	Downregulation of humoral (hypogammaglobulinemia) immune responses by the rituximab induced B-cell depletion
Evidence source(s) and strength of evidence	Infections (including serious infections) are listed in section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects of the SmPC MabThera and are therefore considered as an important identified risk of GP2013.
Characterization of the risk in NHL/CLL indications	Patients with hematological malignancies are often affected by infections, due to an increased susceptibility due the underlying disease or the immunosuppressive treatment. NHL patients have an increased susceptibility to infections; the relative risk for hepatitis C infections is 2-4 fold in patients with B-cell NHL (Grulich and Vajdic 2005).

Infections (including serious infections)	Details System Organ Class (SOC): Infections and infestations
	Relevant for marketing authorizations with indication CLL: CLL patients are susceptible to infections due to the disease-related immunosuppression. About 80% of CLL patients will develop infectious complications at some point of their disease, and more than 50% of patients will die due to infection (Wadhwa and Morrison 2006). As per SmPC MabThera, in patients in clinical trials or during post-marketing surveillance, bacterial and viral infections are very common (≥1/10), and serious viral infections are rare (≥1/10,000 to <1/1,000) in patients with NHL and CLL treated with MabThera monotherapy/maintenance or in combination with chemotherapy. In patients exposed to GP2013, during the GP2013 development program, infections were reported in patients with indolent B-cell NHL and in patients with untreated advanced FL (Table 7-1): • In study GP13-101 in patients with indolent B-cell NHL, 1 patient reported an ADR of infection • In study GP13-301 in patients with untreated advanced FL: • 12.8% of patients reported an ADR of infection during the combination phase 12.2% of patients reported an ADR of infection during the maintenance phase. Serious infections, including fatalities, can occur during therapy with rituximab. Mostly, the infections are of Grade 1 or 2, and patients fully recover. Only limited data are available for patients under 3 years of age. The experience from pediatric DLBCL/BL/BAL/BLL (multicenter, open-label randomized study of Lymphome Malin B chemotherapy (LMB) with or without MabThera in pediatric patients (aged ≥ 6 months to < 18 years old) with previously untreated advanced stage CD20 positive DLBCL/BL/BAL/BLL) showed that the safety profile was generally consistent in type, nature and severity with the known safety profile in adult NHL and CLL patients. Addition of MabThera to chemotherapy did result in an increased risk of some events including infections (including sepsis) compared to chemotherapy only (SmPC MabThera). In patients exposed to GP2013, during the GP2013 development program, no ADR of Grade 3/4 was reported for patients with indolent B-cell NHL. For patients with untreated advanced FL, during the combination phase 2.9% of patients reported ADR of infection of Grade 3/4. This included a single case of Grade 3/4 viral infections (Herpes zoster virus) and of potential viral infections of lower respiratory tract infection or pneumonia. During the maintenance phase, 1.6% of patients reported an ADR of infection of Grade 3/4. This included potential viral infections of Grade 3/4 pneumonia, hepatitis B or respiratory tract infection. As per SmPC MabThera, severe infections were reported in about 4% of patients treated with MabThera monotherapy. Higher frequencies of infections overall, including Grade 3/4 infections, were observed during MabThera maintenance treatment up to 2 years when compared to observation.

Infections (including serious infections)	Details System Organ Class (SOC): Infections and infestations
	For the individual patient, infections can be fatal. Serious infections may severely impact the affected patient. The treatment with rituximab may have to be discontinued.
Characterization of the risk in non-oncology indications	In patients with RA, the incidence of serious infections in patients treated with traditional DMARDs was 39.2 per 1,000 person-years in an observational study (Dixon et al 2007). The rate of infections, in general, is increased in RA compared with other diseases, but more important is the fact that the risk of specific opportunistic infections are increased, such as tuberculosis around fourfold or herpes zoster around twice the risk. The rates are clearly related to both the immunosuppressant drugs used in the treatment of RA, but are also considered to be related to the level of systemic inflammation. Infections account for around 14% of death cases in patients with RA (Carmona et al 2010). In patients in clinical trials or during post-marketing surveillance with RA treated with MabThera infections are very common (≥ 1/10). Infections are more frequent in the first 6 months of treatment. The overall rate of infection was approximately 94 per 100 patient years in rituximab treated patients (SmPC MabThera). In patients with GPA or MPA, in observational studies, 20-60% of patients with ASNCA-associated vasculitis develop infections. Infections in the first year after diagnosis contributed to nearly half of the causes of death. The infection rate is attributed to the immunosuppressive drugs used in the treatment, but the rate is also higher in patients with higher disease activity and impaired renal function (Kronbichler et al 2015). In patients with GPA or MPA treated with MabThera, the overall rate of infection was approximately 237 per 100 patient years (95% CI 197-285) at the 6-month primary endpoint of the clinical trial. In an open-label, single arm study in 25 pediatric patients with severe, active GPA or MPA (overall study period: 6-month remission induction phase with a minimum 18-month follow-up, up to 4.5 years overall). Infections occurred at 17 patients (68%) in the remission induction phase and in 23 patients (92%) in the overall study period. 91% of reported infections were non-serious and 90% were mild to moderate. The most common infections in the overall phase were: upper respiratory tract infections (URTIs) (48%), influenza (24%), conjunctivitis (20%), nasopharyngitis (20%), lower respiratory tract infections (16%), sinusitis (16%), viral URTIs (16%), ear infection (12%), gastroenteritis (12%), pharyngitis (12%), urinary tract infection (12%). Serious infections were reported in 7 patients (28%), and included: influenza (2 patients [8%]) and lower respiratory tract infection (2 patients [8%]) as the most frequently reported events (SmPC MabThera). In patients exposed to GP2013, during the GP2013 development program, infections were reported in patients with RA (Table 7-2): • In study GP13-201, 12.0% of patients experienced an ADR of infection. • In study GP13-302 3.8% of patients experienced an ADR of infection.

Infections (including serious infections)	Details System Organ Class (SOC): Infections and infestations
	Serious infections, including fatalities, can occur during therapy with rituximab. Mostly the infections are of Grade 1 or 2, and patients fully recover. In RA, infections were predominately mild to moderate and consisted mostly of upper respiratory tract infections and urinary tract infections. The incidence of infections that were serious or required IV antibiotics was approximately 4 per 100 patient years. The rate of serious infections did not show any significant increase following multiple courses of rituximab (SmPC MabThera). In GPA and MPA, infections were predominately mild to moderate and consisted mostly of upper respiratory tract infections, herpes zoster and urinary tract infections. The rate of serious infections was approximately 25 per 100 patient years. The most frequently reported serious infection in the rituximab group was pneumonia at a frequency of 4% (SmPC MabThera). In PV infections are predominantly dermal and consist of mostly complications attributable to disruption of the epidermal barrier due to the disease itself and immunosuppression induced by treatment (Esmaili 2013). For the individual patient, infections can be fatal. Serious infections may severely impact the affected patient. The treatment with rituximab may have to be discontinued.
Risk factors and risk groups	Patients are at risk who present with a history of recurring or chronic infections or with underlying conditions, which may further predispose patients to serious infection. More chemotherapeutic or immunosuppressive agents, longer periods of chemotherapy or immunosuppression, or repeated rounds of chemotherapy are also risks for serious infections, serious viral infections and opportunistic infections. Additionally, patients with hematological cancers, such as NHL, may have a constitutive immunodeficiency, which is intensified by the different treatment regimens and old age (Takata et al 2009).
Preventability	Active severe infections are a contra-indication for the treatment with Rixathon / Riximyo. Rixathon / Riximyo 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 (Cluster of Differentiation 8) are very low). Physicians should exercise caution when considering the use of Rixathon / Riximyo in patients with a history of recurring or chronic infections or with underlying conditions that may further predispose patients to serious infection, e.g. hypogammaglobulinemia. It is recommended that immunoglobulin levels are determined prior to initiating treatment with Rixathon / Riximyo. Patients should be monitored for signs and symptoms of infection and treated appropriately, as per age and local specific guidelines. Before giving a subsequent course of Rixathon / Riximyo treatment, patients should be re-evaluated for any potential risk for infections.
Impact on the benefit-risk balance of the product	The totality of the evidence established similarity of GP2013 to the reference product MabThera in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability

Infections (including serious infections)	Details System Organ Class (SOC): Infections and infestations
	exercise as required by CHMP/437/04 Rev 1. Overall, the results of the global development program confirm that GP2013 is biosimilar to the reference product MabThera and has a similar and positive benefit-risk ratio
Public health impact	Impact is low to moderate with prompt and appropriate treatment.

All indications Important Identified Risk: Progressive multifocal leukoencephalopathy (PML)

During the clinical development of GP2013, no case of PML was reported.

Table 7-4 All indications: Important identified risk progressive multifocal leukoencephalopathy (PML): Other details

Progressive multifocal leukoencephalo-pathy	Details PTs: Human polyomavirus infection, JC polyomavirus test positive, JC virus CSF test positive, JC virus granule cell neuronopathy, JC virus infection, Leukoencephalomyelitis, Leukoencephalopathy, Polyomavirus test positive, Progressive multifocal leukoencephalopathy
Potential mechanisms	Reactivation of latent JC polyoma virus due to immunosuppressive effect of rituximab, up to 92% of the adult population is JCV-seropositive (Carson et al 2009).
Evidence source(s) and strength of evidence	PML is listed in section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects of the SmPC MabThera and is therefore considered as an important identified risk of GP2013.
Characterization of the risk:	No clear incidence data specific for the NHL/CLL population were identified. Data on PML in patients with RA were obtained from a nationwide inpatient sample, representing 20% of all US hospital discharges. When patients with other potential risk factors for PML (HIV, malignancy, bone marrow or other organ transplantation) were excluded, the rates of PML per 100,000 discharges coded for RA were 0.4, compared with a rate of PML in the background population of 0.2/100,000 discharges (Molloy and Calabrese 2009). For patients with GPA or MPA, a background incidence in patients not treated with rituximab could not be identified. During the clinical development of GP2013, no case of PML was reported. Very rare cases (<10/10,000) of fatal PML have been reported following use of rituximab. Only limited data are available for patients under 3 years of age (SmPC MabThera). PML is general an often severe condition. The case-fatality rate was 90%: 100% among PML cases diagnosed within 3 months of the last rituximab dose versus 84% among PML cases diagnosed more than 3 months after the last rituximab dose (Carson et al 2009). For the individual patient, PML has a substantial impact on the quality of life. PML symptoms worsen over time with progressive CNS demyelination and multiple neurological symptoms (e.g. confusion/disorientation, motor

Progressive multifocal leukoencephalo-pathy	**Details** PTs: Human polyomavirus infection, JC polyomavirus test positive, JC virus CSF test positive, JC virus granule cell neuronopathy, JC virus infection, Leukoencephalomyelitis, Leukoencephalopathy, Polyomavirus test positive, Progressive multifocal leukoencephalopathy
	weakness/hemiparesis, poor motor coordination, speech changes, or vision changes). The safety profile of MabThera in pediatric DLBCL/BL/BAL/BLL as well as GPA or MPA patients was generally consistent in type, nature and severity with the known safety profile in adult patients in the approved autoimmune indications, including adult GPA or MPA (SmPC MabThera).
Risk factors and risk groups	There are currently no known risk groups or risk factors for the development of PML associated with rituximab. PML general occurs in patients with suppressed cellular immunity. More immunosuppressive agents, longer periods of immunosuppression or repeated rounds of immunotherapy are also risks for serious infections, serious viral infections and opportunistic infections. Additionally, patients with hematological cancers, such as NHL, may have a constitutive immunodeficiency, which is intensified by the different treatment regimens and old age (Takata et al 2009). In GPA/MPA patients the use of cyclophosphamide is an additional risk factor for development of PML.
Preventability	No data are available that can be used to prevent PML associated with rituximab.
Impact on the benefit-risk balance of the product	The totality of the evidence established similarity of GP2013 to the reference product MabThera in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise as required by CHMP/437/04 Rev 1. Overall, the results of the global development program confirm that GP2013 is biosimilar to the reference product MabThera and has a similar and positive benefit-risk ratio.
Public health impact	Public health impact is considered to be low to moderate.

7.3.2 SVII.3.2. Presentation of the missing information

None.

8 Part II Safety specification Module SVIII: Summary of the safety concerns

Table 8-1 Table Part II SVIII.1: Summary of safety concerns

Important identified risks	Infections (including serious infections) (all indications) Progressive multifocal leukoencephalopathy (PML) (all indications)
Important potential risks	None
Missing information	None

9 Part III: Pharmacovigilance plan (including post-authorization safety studies)

9.1 Part III.1. Routine pharmacovigilance activities

The Global Pharmacovigilance System ensures the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

9.1.1 Routine pharmacovigilance activities beyond ADRs reporting and signal detection

There are no other routine pharmacovigilance activities beyond ADRs reporting and signal detection.

9.2 Part III.2. Additional pharmacovigilance activities

None.

9.3 Part III.3. Summary Table of additional pharmacovigilance activities

Table 9-1 Part III.1: Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
None				

10 Part IV: Plans for post-authorization efficacy studies

There are no planned post-authorization efficacy studies.

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

Risk Minimization Plan

11.1 Part V.1. Routine risk minimization measures

Table 11-1 Table Part V.1: Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Infections (including serious infections) (All indications)	**Routine risk communication** SmPC sections 4.3 Contraindications, 4.4 Special warnings and precautions for use and 4.8 Undesirable effects. Package Leaflet (PL) sections 2. What you need to know before you are given Rixathon / Riximyo and 4. Possible side effects. Routine risk minimization activities recommending specific clinical measures: In SmPC section 4.4 Special warnings and precautions for use recommendation for monitoring of patients at regular intervals for any symptoms or signs that may be suggestive of PML and respective therapy and diagnostic advices. Recommendation of caution when considering the use of Rixathon / Riximyo in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection. Recommendation of Hepatitis B virus (HBV) screening in all patients before initiation of treatment with Rixathon / Riximyo, of consultation of a liver disease expert for patients with positive hepatitis B serology and of monitoring and management following local medical standards to prevent hepatitis B reactivation. In PL section 4 Possible side effects recommendation to reach out to the doctor immediately if there are signs of an infection including fever, cough, sore throat, burning pain when passing urine or feeling weak or generally unwell is included Other routine risk minimization measures beyond the Product Information: Legal status: Prescription only
Progressive multifocal leukoencephalopathy (PML) (All indications)	**Routine risk communication** SmPC sections 4.4 Special warnings and precautions for use and 4.8 Undesirable effects PL section 4. Possible side effects Routine risk minimization activities recommending specific clinical measures: Recommendation for monitoring of patients at regular intervals and suspension of further dosing if PML is suspected, in case of doubt considering further evaluation including MRI scan preferably with

Safety concern	Routine risk minimization activities
	contrast, cerebrospinal fluid (CSF) testing for JC Viral DNA and repeat neurological assessments. and permanently discontinuing dosing of Rixathon / Riximyo if a patient develops PML is included in SmPC section 4.4 Special warnings and precautions for use. In PL section 4 Possible side effects recommendation to reach out to the doctor immediately if there are signs of an infection including memory loss, trouble thinking, difficulty walking or sight loss – these may be due to a very rare, serious brain infection, which has been fatal (Progressive Multifocal Leukoencephalopathy or PML) have been included. Other routine risk minimization measures beyond the Product Information: Legal status: Prescription only

11.2 Part V.2. Additional Risk minimization measures

Patient alert card

Objectives:

To minimize the occurrence and severity of

- Infections (including serious infections)

- Progressive multifocal leukoencephalopathy (PML).

Rationale for the additional risk minimization activity:

Patients to understand the risk of infections (including serious infections) and PML and appropriate management of these conditions.

Target audience and planned distribution path:

The patient alert card is part of the product information in the outer packaging. HCPs are instructed to hand out the patient alert card prior to each Rixathon / Riximyo infusion for non-oncology indications.

Plans to evaluate the effectiveness of the interventions and criteria for success:

AE reports are reviewed on an on-going basis and appropriate action taken as needed.

Frequency and severity of AEs due to infections (including serious infections) and PML are the primary indicator. Post-marketing AE profiles are compared with the expected AE profiles.

An evaluation of the effectiveness of risk minimization measures is done in PSURs on the basis of all collected safety information. A conclusion of the appropriateness of the current safety profile and a possible need for changes to risk minimization is presented therein.

Rationale for removal of the additional risk minimization measures

In alignment with the reference product MabThera RMP 25.1 as suggested in PRAC PSUR assessment report for Procedure EMEA/H/C/PSUSA/00002652/202311, MAH removed the additional risk minimization measures HCP educational leaflet, Patient educational leaflet and HCP alert card.

11.3 Part V.3. Summary of risk minimization measures

Table 11-2 Summary of pharmacovigilance activities and risk minimization activities by safety concerns

Safety concern	Risk minimization measures	Pharmacovigilance activities
Infections (including serious infections) (All indications)	Routine risk minimization measures: SmPC sections 4.3, 4.4 and 4.8; section 4.4 where recommendation for exercising caution when considering the use of rituximab in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection is included PL sections 2 and section 4 where recommendation to reach out to the doctor immediately if there are signs of an infection including fever, cough, sore throat, burning pain when passing urine or feeling weak or generally unwell is included Legal status: Prescription only Additional risk minimization measures (For non-oncology indications): Patient alert card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
PML (All indications)	Routine risk minimization measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and

Safety concern	Risk minimization measures	Pharmacovigilance activities
	SmPC sections 4.4 and 4.8; section 4.4 where recommendation for monitoring of patients at regular intervals and suspension of further dosing if PML is suspected. In case of doubt, considering further evaluation including MRI scan preferably with contrast, cerebrospinal fluid (CSF) testing for JC Viral DNA and repeat neurological assessments and permanently discontinuing dosing of Rixathon / Riximyo if a patient develops PML is included PL section 4 recommendation to reach out to the doctor immediately if there are signs of an infection including memory loss, trouble thinking, difficulty walking or sight loss – these may be due to a very rare, serious brain infection, which has been fatal (Progressive Multifocal Leukoencephalopathy or PML) have been included Legal status: Prescription only Additional risk minimization measures (for non-oncology indications): Patient alert card	signal detection: None Additional pharmacovigilance activities: None

12 Part VI: Summary of the risk management plan for Rixathon / Riximyo (rituximab)

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

Rixathon's / Riximyo's summaries of product characteristics (SmPC) and their package leaflets give essential information to healthcare professionals and patients on how Rixathon / Riximyo should be used.

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

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

12.1 Part VI: I. The medicine and what it is used for

Rixathon / Riximyo is authorized for use in adults to treat the following blood cancers and inflammatory conditions (see SmPCs for the full indication):

- follicular lymphoma and diffuse large B cell non-Hodgkin's lymphoma (two types of non-Hodgkin's lymphoma, a blood cancer);
- chronic lymphocytic leukemia (CLL, another blood cancer affecting white blood cells);
- granulomatosis with polyangiitis (GPA or Wegener's granulomatosis) and microscopic polyangiitis (MPA), which are inflammatory conditions of the blood vessels;
- pemphigus vulgaris;
- for Rixathon only: severe rheumatoid arthritis (an inflammatory condition of the joints).

Rixathon / Riximyo is authorized for use in paediatric patients to treat the following:

- in 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)
- in paediatric patients (aged ≥ 2 to < 18 years old) with severe, active GPA (Wegener's) and MPA.

It contains rituximab as the active substance, and it is given by intravenous infusion.

Further information about the evaluation of Rixathon's / Riximyo's benefits and risks can be found in Rixathon's / Riximyo's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

Rixathon: https://www.ema.europa.eu/en/medicines/human/EPAR/rixathon

Riximyo: https://www.ema.europa.eu/en/medicines/human/EPAR/riximyo

12.2 Part VI: II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Rixathon / Riximyo, together with measures to minimize such risks and the proposed studies for learning more about Rixathon's / Riximyo's risks, are outlined below.

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

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The 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 minimize its risks.

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

In the case of Rixathon / Riximyo, these measures are supplemented with *additional risk minimization 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*.

12.2.1 Part VI – II.A: List of important risks and missing information

Important risks of Rixathon / Riximyo are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Rixathon / Riximyo. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 12-1 List of important risks and missing information

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

12.2.2 Part VI – II.B: Summary of important risks

Table 12-2 All indications: Important identified risk 'Infections (including serious infections)'

Evidence for linking the risk to the medicine	Infections (including serious infections) are listed in section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects of the SmPC MabThera and are therefore considered as an important identified risk of GP2013.
Risk factors and risk groups	Patients are at risk who present with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection.
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.3, 4.4 and 4.8; section 4.4 where recommendation for exercising caution when considering the use of rituximab in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection is included PL section 2 and in PL section 4 Possible side effects recommendation to reach out to the doctor immediately if there are signs of an infection including fever, cough, sore throat, burning pain when passing urine or feeling weak or generally unwell is included Legal status: Prescription only Additional risk minimization measures (for non oncology indication): Patient alert card

Table 12-3 All indications: Important identified risk 'Progressive multifocal leukoencephalopathy (PML)'

Evidence for linking the risk to the medicine	PML is listed in section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects of the SmPC MabThera and is therefore considered as an important identified risk of GP2013.
Risk factors and risk groups	There are currently no known risk groups or risk factors for the development of PML associated with rituximab. PML general occurs in patients with suppressed cellular immunity.
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.4 and 4.8; section 4.4 where recommendation for monitoring of patients at regular intervals and suspension of further dosing if PML is suspected, in case of doubt considering further evaluation including MRI scan preferably with contrast, cerebrospinal fluid (CSF) testing for JC Viral DNA and repeat neurological assessments and permanently discontinuing dosing of Rixathon / Riximyo if a patient develops PML is included PL section 4 Possible side effects recommendation to reach out to the doctor immediately if there are signs of an infection including memory loss, trouble thinking, difficulty walking or sight loss – these may be due to a very rare, serious brain infection, which has been fatal (Progressive Multifocal Leukoencephalopathy or PML) have been included. Legal status: Prescription only

	Additional risk minimization measures: (for non oncology indication): Patient alert card

12.2.3 Part VI – II.C: Post-authorization development plan

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

There are no studies which are conditions of the marketing authorization or specific obligation of Rixathon / Riximyo.

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

None.

13 Part VII: Annexes

Table of contents

Annex 1 – EudraVigilance Interface

Available in electronic format only.

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

Table 13-1 Completed studies

Study	Summary of objectives	Safety concerns addressed	Date of Final Study Report submission / Study report
GP13-201 Part II: A randomized, double-blind, controlled study to evaluate pharmacokinetics, pharmacodynamics, safety and efficacy of GP2013 and rituximab in patients with rheumatoid arthritis refractory or intolerant to standard DMARDs and one or up to three anti-TNF therapies Category 3	Primary objective: To assess Bioequivalence between GP2013 and rituximab Safety objectives: - Overall safety and tolerability - Incidence of anti-drug antibodies	Immunogenicity, infections (including serious infections)	Part I: Was part of the submission for marketing authorization in Apr 2016 Part II: 24 week interim report: Dec 2016 (finalized) 52 week final report: Jan 2018
GP13-302: A randomized, double-blind, controlled, parallel-group, multicenter study to assess the safety and immunogenicity of transitioning to GP2013 or re-treatment with Rituxan® or MabThera® in patients with active rheumatoid arthritis, previously treated with Rituxan® or MabThera® Category 3	Identify potential safety risk of the transition from reference product to GP2013 as compared to continuing with respective treatment weight	Immunogenicity, infections (including serious viral infections)	12 week interim report: Aug 2017 (finalized) 24 week report: Jan 2018
GP13-301: A randomized, controlled, double-blind Phase III trial to compare the efficacy, safety and pharmacokinetics of GP2013 plus cyclophosphamide,	Primary objective: To demonstrate comparability of the overall response rate (ORR) Safety objectives: - Safety of GP2013 in comparison to	Infections (including serious infections), serious viral infections, opportunistic infections.	Combination phase (cut-off date 10-Jul-2015): Was part of the submission for marketing authorization in Apr 2016 Interim Analysis (cut-off date 10-Jul-2016): Dec 2016 (finalized) Final report: 13-Nov-2018

Study	Summary of objectives	Safety concerns addressed	Date of Final Study Report submission / Study report
vincristine, prednisone vs. MabThera® plus cyclophosphamide, vincristine, prednisone, followed by GP2013 or MabThera® maintenance therapy in patients with previously untreated, advanced stage follicular lymphoma Category 3	MabThera® either as single agent or in combination with CVP - Incidence of immunogenicity (anti-drug antibody formation)		

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

Part A: Requested protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this first or updated version of the RMP.

None

Part B: Requested amendments of previously approved protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP.

None

Part C: Previously agreed protocols for ongoing studies and final protocols not reviewed by the competent authority.

Approved protocols: None

Final protocols not reviewed or approved: None.

Annex 4 - Specific adverse drug reaction follow-up forms

None

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

Not applicable

Annex 6 - Details of proposed additional risk minimization activities (if applicable)

Approved key messages of the additional risk minimization measures

For non-oncology indications:

A Patient Alert Card will be included in the carton.

The Patient Alert Card for Rixathon® / Riximyo® contains 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

As the Patient Alert Card is part of the product information in the outer packaging, the content will be centrally approved for all EU/EEA languages without need of further approval by National Authorities.

Annex 7 - Other supporting data (including referenced material)

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[Module 5.3.3.2 GP13-101] Phase I Trial to Assess the Safety and Pharmacokinetics of GP2013 Monotherapy Administered Weekly in Japanese Patients with CD20 Positive Low Tumor Burden Indolent B cell Non-Hodgkin's Lymphoma. Report date 25-Feb-2015.

[Module 5.3.3.2 GP13-201 Part I], [Module 5.3.3.2 GP13-201 Part II] A randomized, double-blind, controlled study to evaluate pharmacokinetics, pharmacodynamics, safety and efficacy of GP2013 and rituximab in patients with rheumatoid arthritis refractory or intolerant to standard DMARDs and one or up to three anti-TNF therapies. Report date 09-Dec-2015 (Part I), 11-Sep-2017 (Part II).

[Module 5.3.5.1 GP13-301 Primary Analysis], [Module 5.3.5.1 GP13-301 First Interim Analysis], [Module 5.3.5.1 GP13-301 Final Analysis] A randomized, controlled, double-blind Phase III trial to compare the efficacy, safety and pharmacokinetics of GP2013 plus cyclophosphamide, vincristine, prednisone vs. MabThera® plus cyclophosphamide, vincristine, prednisone, followed by GP2013 or MabThera® maintenance therapy in patients with previously untreated, advanced stage follicular lymphoma. Report date 04-Feb-2016 (Primary Analysis), 12-Dec-2016 (First Interim Analysis), 13-Nov-2018 (Final Analysis).

[Module 5.3.5.1 GP13-302 24 weeks] A randomized, double- blind, controlled, parallel-group, multicenter study to assess the safety and immunogenicity of transitioning to GP2013 or re-treatment with Rituxan® or MabThera® in patients with active rheumatoid arthritis, previously treated with Rituxan® or MabThera®. Report date 12-Jul-2017 (24 weeks).

[Module 5.3.5.4 CGP2013ES01R] Rapid intravenous infusion of rituximab biosimilar, Rixathon. A retrospective non-interventional post-authorisation safety study in Spain. Report date 01-Jun-2022.

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

Table 13-2 Summary of changes to the risk management plan over time

Version	Approval date Procedure	Change
2.0	Approval date: 25-Sep-2017 Procedure numbers: EMEA/H/C/003903/IB/0005; EMEA/H/C/004729/IB/0005	Update of due dates for Part II 52 weeks study report for GP13-201, final study report for GP13-301 and 12 and 24 week study report for GP13-302 in all relevant tables of the RMP Affected safety concerns: Important identified risks: Infusion related reactions (for all indications) Infections (including serious infections) (for all indications) Serious viral infections (for NHL/CLL) Neutropenia (including prolonged) (for all indications) Important potential risk: Opportunistic infections (for all indications) Missing information: Immunogenicity (for RA, GPA/MPA)
3.0	Approval date: not applicable Procedure number: Available after accepted submission by EMA	Transfer of RMP v.2.0 from the old into the new EMA RMP template Update of the Pharmacovigilance Plan and all other relevant RMP parts related to: Study GP13-201: • Removed as study has been completed and obligation has been fulfilled Study GP13-302: • Removed as study has been completed and obligation has been fulfilled
3.1	Approval date: 12-Jul-2018 Procedure number: EMEA/H/C/xxxx/WS/1335	Correction due to Type II variation assessment report on Procedure No. EMEA/H/C/WS1335 requested by CHMP No significant changes; only formal updates.
4.0	Approval date: not applicable Procedure number: Available after accepted submission by EMA	Based on type II variation CHMP Rapporteur's preliminary assessment report and PRAC Rapporteur's assessment report in EMEA/H/C/WS1335 and the requested critical risk assessment: - MAH proposed in the latest PSUR covering the period 18-Nov-2017 to 17-Nov-2018 deletion of important identified/potential risks Tumor Lysis Syndrome, Stevens-Johnson Syndrome / Toxic Epidermal Necrolysis, Gastrointestinal perforation in oncology indications, Infusion-related reactions, Neutropenia(including prolonged), HBV reactivation, Administration route error, Hypogammaglobinemia, Adverse events in patients >70

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		years. Use in pregnancy and lactation (Missing information): Given provision of established language for this concern in the label, the MAH proposed that these risks / missing information revert to standard pharmacovigilance and deleted them from the RMP safety profile. The MAH also proposed that the risk titled in prior documents 'Impact on cardiovascular disease' change to 'Worsening of pre-existing cardiovascular disorders'. Update of the Pharmacovigilance Plan and all other relevant RMP parts related to GP13-301 as the study has been completed and the obligation fulfilled.
4.1	Approval date: 05-Sep-2019 Procedure number: EMEA/H/C/003903/WS1599; EMEA/C/C/004729/WS1599	Change based on the PRAC type II variation assessment report dated 16-May-2019, receipt of the updated MabThera RMP (v.19.1), a related re-evaluation of the risk profile and submission of application for the new indication pemphigus vulgaris: Deletion of important identified risks - Serious viral infections (after critical analysis subsumed in the Risk on Serious infections) - Impaired immunization response (after critical analysis is adequately labeled) Deletion of important potential risks - Opportunistic infections (after critical analysis subsumed in the Risk on Serious infections) - Posterior reversible encephalopathy syndrome (after critical analysis, this item is adequately labeled) - Prolonged B-cell depletion (after critical analysis this item is adequately labeled) - Second malignancies (after critical analysis this item is adequately labeled) Inclusion of important identified risks - Hypogammaglobulinemia (non-oncology indications) - Hepatitis B reactivation (all indications) Inclusion of important potential risk - Administration route error (NHL/CLL) Inclusion of missing information - Use in pregnancy and lactation. Summary of risks applicable for all indications, for non-oncology indications. Update of safety concerns covered by European registries BSRBR, ARTIS, and RABBIT

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		Inclusion of targeted FU questionnaire for Hepatitis B reactivation Inclusion of HCP alert Card for Administration route error Inclusion of pemphigus vulgaris as new indication.
5.0	Approval date: not applicable Procedure number: Available after accepted submission by EMA	On request in the PRAC Rapporteur's preliminary assessment report on PSUR P3, dated 07-Apr-2020, (EMEA/H/C/PSUSA/00002652/201911) to align the RMP summary of safety concerns with the latest approved RMP for MabThera v21.1: Deletion of important potential risks: - Acute myeloid leukemia / Myelodysplastic syndrome (NHL/CLL), - Gastrointestinal perforation (non-oncology indications - Off-label use in autoimmune disease (non-oncology indications) Deletion of missing information: - Immunogenicity and autoimmune disease (non-oncology indications). Due to the intended new marketing authorization for respective indications in the pediatric population following their approval for MabThera, the MAH also deleted the important potential risk 'Off-label use in pediatric patients' (all indications) from the risk profile. Deletion of targeted follow-up questionnaire for off-label use in paediatric population The following new indications were added: • 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) • 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. Registry milestones were updated. Post-authorization exposure updated Annex 4 updated to update the follow-up questionnaires for PML and Malignancy and Neoplasm Limitations to detect adverse reactions in clinical trial development programs updated to include the pediatric indications

Version	Approval date Procedure	Change
		Routine risk minimization measures updated Update of new scientific information in tables of Part II Module SVII.3 Details of important identified risks, important potential risks, and missing information.
5.1	Approval date: 23-Aug-2020 Procedure number: EMEA/H/C/003903/IB/0041 EMEA/H/C/004729/IB/0041	Update based on the PRAC request for supplementary information dated 25-Jun-2020.
6.0	Approval date: 20-Aug-2021 Procedure number: EMEA/H/C/003903/IB/0051; EMEA/H/C/004729/IB/0052	Based on the recommendation from the Pharmacovigilance Risk Assessment Committee (PRAC) Assessment Report on the PSUR covering the reporting period 18-Nov-2019 – 17-Nov-2020 (Procedure number: EMEA/H/C/PSUSA/00002652/202011), dated 10-Jun-2021, the MAH Sandoz was requested to remove RABBIT, BSRBR, and ARTIS registries from the RMP with the next regulatory opportunity and not later than with the next PSUR. These studies were also removed from the innovator RMP (Mabthera - Roche) during procedure EMEA/H/C/000165/II/0168, which was finalized on 03 Mar 2020. A summary of the study results should be presented and discussed with the next PSUR. According to this request, the registries RABBIT, BSRBR, and ARTIS are being removed from RMP v.6.0, and the study results will be reviewed in the next applicable PSUR following receipt of final study reports. Based on this recommendation, the MAH will also step out of negotiations for participation in the ARTIS registry. Updated the approved indications for Riximyo to include RA. Alignment of safety profile to EPAR RMP summary for the reference product MabThera, updated on 16 Oct 2020: Deletion of important potential risks ‘Malignant events’ (non-oncology indications), ‘Worsening of pre-existing cardiovascular disorders’ (non-oncology indications) and missing information ‘Use in pregnancy and lactation’ (all indications). Deletion of targeted follow-up questionnaire for ‘Malignant events’ (non-oncology indications). Updated the follow-up questionnaire for PML.
7.0	Approval date: not applicable Procedure number: Available after submission accepted by EMA	Post-authorization exposure was updated. Annex 7: Statistical methods description and outputs were removed in line with the EU RMP template

Version	Approval date Procedure	Change
7.1	Approval date: 27 Feb 2023 Procedure number: EMEA/H/C/WS2307	Update based on the PRAC request for supplementary information dated 15-Sep-2022 as follows: • Deletion of the important potential risk 'Relapses' (for GPA/MPA) • Inclusion of a statement that no safety concerns have been identified in relation to the 90-minute infusion regimen for NHL and CLL indications • Update of post-authorization exposure and removal of the term 'USA'in the corresponding table. Update of the EPAR links in Part VI
8.0	Approval date: Not applicable Procedure number: Available after submission accepted by EMA	Updated based on PRAC PSUR assessment report for Procedure EMEA/H/C/PSUSA/00002652/202311 dated 30 May 2024, where, MAH is obliged to align the current RMP v.7.1 with reference product MabThera RMP v.25.1. • Updated Part I for ATC code and additional monitoring in EU. • Updated Part II for post authorization exposure and deletion of safety concerns as below: *Important Identified Risk* 1. Hepatitis B (HBV) reactivation (all indications) 2. Hypogammaglobulinemia (non-oncology indications)' *Missing Information* 1. Long-term use in GPA/MPA patients (GPA/MPA) • Removed details for additional risk minimization measures HCP educational leaflet, Patient educational leaflet and TFUQ.
8.1	Approval date: not applicable Procedure number: Available after submission accepted by EMA	Updated based on Committee for Medicinal Products for Human Use (CHMP) Type IB work sharing (WS) variation assessment report for procedure EMA/VR/0000249103 dated 24 Apr 2025. • As per new information in SmPC, updated the information in 'pharmacotherapeutics group', 'Information about its composition', 'Indication' and 'Dosage'. • Part II-SVII: Removed important potential risk "administration route error (NHL/CLL)". • Part II-SVIII: Removed important potential risk "administration route error (NHL/CLL)" from summary of safety concerns.

Version	Approval date Procedure	Change
		• Part V: Removed information for important potential risk “administration route error (NHL/CLL)” and HCP alert card. • Part VI: Updated in line with the changes to Part II and Part V. • Part VII: Updated in line with the changes to the above parts.