SANDOZ A Novartis Division

Chief Medical Office & Patient Safety

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

722-0133-182-967-3-1

Summary of the 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 of the RMP Public Summary:	3.1
Date of final sign off of the RMP Public Summary:	18-Jul-2018

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The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimize them. The RMP summary of Rixathon / Riximyo is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the “Arzneimittelinformation / Information sur le médicament” approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Note that the reference document that is valid and relevant for the effective and safe use of Rixathon in Switzerland is the “Arzneimittelinformation / Information sur le médicament” (see www.swissmedicinfo.ch) approved and authorized by Swissmedic. Sandoz Pharmaceuticals AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Rixathon / Riximyo.

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

This is a summary of the risk management plan (RMP) for Rixathon / Riximyo. 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.

1.1 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);
- for Rixathon only: chronic lymphocytic leukemia (CLL, another blood cancer affecting white blood cells);
- severe rheumatoid arthritis (an inflammatory condition of the joints);
- granulomatosis with polyangiitis (GPA or Wegener's granulomatosis) and microscopic polyangiitis (MPA), which are inflammatory conditions of the blood vessels.

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: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003903/WC500232462.pdf

Riximyo: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004729/WC500232539.pdf

1.2 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*.

If important information that may affect the safe use of Rixathon / Riximyo is not yet available, it is listed under 'missing information' below.

1.2.1 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 1-1 List of important risks and missing information

List of important risks and missing information	
Important identified risks	**NHL/CLL** Infusion-related reactions Infections (including serious infections) Serious viral infections Impaired immunization response Progressive multifocal leukoencephalopathy (PML) Neutropenia (including prolonged) Hepatitis B virus (HBV) reactivation Tumor lysis syndrome Gastrointestinal (GI) perforation Stevens-Johnson syndrome (SJS)/Toxic epidermal necrolysis (TEN) **RA** Infusion-related reactions Infections (including serious infections)

List of important risks and missing information	
	Impaired immunization response
	PML
	Neutropenia (including prolonged)
	HBV reactivation
	Hypogammaglobulinemia
	SJS / TEN
	GPA/MPA
	Infusion-related reactions
	Infections (including serious infections)
	Impaired immunization response
	PML
	Neutropenia (including prolonged)
	HBV reactivation
	Hypogammaglobulinemia
	SJS / TEN
Important potential risks	**NHL/CLL**
	Posterior reversible encephalopathy syndrome (PRES)
	Opportunistic infections
	Prolonged B-cell depletion
	Increased risk of Grade 3/4 serious blood and lymphatic system Adverse Events (AEs) in patients >70 years (applicable for CLL only / relevant for marketing authorizations with indication CLL)
	Acute myeloid leukemia (AML)/Myelodysplastic syndrome (MDS)
	Second malignancies
	Off-label use in pediatric patients
	Administration route error
	RA
	PRES
	Opportunistic infections
	Malignant events
	Impact on cardiovascular disease
	Gastrointestinal (GI) perforation
	Prolonged B-cell depletion
	Off-label use in autoimmune disease
	Off-label use in pediatric patients
	GPA/MPA
	PRES
	Opportunistic infections
	Malignant events
	Impact on cardiovascular disease
	GI perforation
	Prolonged B-cell depletion
	Off-label use in autoimmune disease
	Off-label use in pediatric patients
	Relapses

List of important risks and missing information	
Missing information	**NHL/CLL** Use in pregnancy and lactation **RA** Use in pregnancy and lactation Immunogenicity and autoimmune disease **GPA/MPA** Use in pregnancy and lactation Immunogenicity and autoimmune disease Long-term use in GPA/MPA patients

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

Table 1-2 NHL/CLL: Important identified risk infusion-related reactions

Evidence for linking the risk to the medicine	Infusion-related reactions 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 with a high tumor burden or with a high number (≥25 × 10^9/L) of circulating malignant cells such as patients with CLL, who may be at higher risk of especially severe cytokine release syndrome, should only be treated with extreme caution [relevant for marketing authorizations with indication CLL]. Patients with a history of pulmonary insufficiency or those with pulmonary tumor infiltration may be at greater risk of poor outcome and should be treated with increased caution.
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.2, 4.4 and 4.8; sections 4.2 and 4.4 give recommendations for pre-medication, management of infusion-related reactions and monitoring of patients; PL section 4 which also describes infusion modifications in case of infusion-related reactions Legal status: Prescription only
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study GP13-301 See section 2.3 of this summary for an overview of the post-authorization development plan.

Table 1-3 NHL/CLL: 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; setion 4.4 where recommendation for exercising caution when considering the use of rituximab in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection is included PL sections 2 and 4 Legal status: Prescription only
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study GP13-301 See section 2.3 of this summary for an overview of the post-authorization development plan.

Table 1-4 NHL/CLL: Important identified risk serious viral 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 sections 2 and 4 Legal status: Prescription only
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study GP13-301 See section 2.3 of this summary for an overview of the post-authorization development plan.

Table 1-5 NHL/CLL: Important identified risk impaired immunization response

Evidence for linking the risk to the medicine	Immunisations are listed in section 4.4 Special warnings and precautions for use of the SmPC MabThera and are therefore considered as an important identified risk of GP2013.
Risk factors and risk groups	Relevant for marketing authorizations with indication CLL: Patients with CLL are at special risk due to their impaired immunization response resulting from the bone marrow infiltration by the underlying disease and from sequel from myelotoxic treatment including immunoglobulin deficiency.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.4 which gives recommendation that patients treated with Rixathon / Riximyo may receive non-live vaccinations, vaccination with live virus vaccines is not recommended PL section 2 Legal status: Prescription only

Table 1-6 NHL/CLL: 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 4.3, 4.4 and 4.8; section 4.4 where recommendation for monitoring of patients at regular intervals and suspension of further dosing if PML is suspected, considering further evaluation and permanently discontinuing dosing of Rixathon / Riximyo if a patient develops PML is included PL section 4 Legal status: Prescription only

Table 1-7 NHL/CLL: Important identified risk neutropenia (including prolonged)

Evidence for linking the risk to the medicine	Neutropenia is listed in 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	Patients with underlying malignancies and previous myelotoxic therapy are at increased risk. The risk of infections due to neutropenia is greater in malignancies than in autoimmune diseases. Patients considered at increased risk of late-onset neutropenia include patients after autologous stem cell transplantation, patients treated for acquired immunodeficiency syndrome (AIDS)-related lymphoma, and patients treated with purine analogues.
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.4 and 4.8; section 4.4 where recommendation for performing regular full blood counts is included; PL section 4 Legal status: Prescription only
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study GP13-301 See section 2.3 of this summary for an overview of the post-authorization development plan.

Table 1-8 NHL/CLL: Important identified risk hepatitis B virus (HBV) reactivation

Evidence for linking the risk to the medicine	HBV reactivation 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	The majority of patients developing a HBV reactivation during treatment with rituximab were also exposed to chemotherapy. Pre-chemotherapy HBV DNA level and the use of steroids were also considered as risk factors.

Risk minimization measures	Routine risk minimization measures: SmPC section 4.4 and 4.8; section 4.4 where recommendation for HBV screening before initiation of treatment with Rixathon / Riximyo is included; PL sections 2 and 4 Legal status: Prescription only

Table 1-9 NHL/CLL: Important identified risk tumor lysis syndrome

Evidence for linking the risk to the medicine	Tumor lysis snydrome 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	A high number of circulating malignant cells (≥25,000/mm3) or high tumor burden confers a risk of tumor lysis syndrome. Further risk factors for developing acute tumor lysis syndrome after initiation of therapy in all tumors are uric acid level > 7.5 mg/dL at initiation of treatment, underlying renal insufficiency, creatinine >1.6 mg/dL, hypercalcemia, bulky disease, high LDH, and high tumor growth fraction.
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.2, 4.4 and 4.8; section 4.2 where recommendation for administration of prednisone/prednisolone 100 mg intravenous shortly before infusion with Rixathon / Riximyo in CLL patients whose lymphocyte counts are >25 × 10^9/L and evaluation for evidence of tumor lysis syndrome in NHL patients is included; sections 4.4 and 4.8 PL section 4 Legal status: Prescription only

Table 1-10 NHL/CLL: Important identified risk gastrointestinal (GI) perforation

Evidence for linking the risk to the medicine	GI perforation is listed for patients with NHL or CLL in 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	In the majority of these cases, rituximab was administered with chemotherapy. Also patients with gastrointestinal lymphoma lesions are at increased risk.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.8 PL section4 Legal status: Prescription only

Table 1-11 NHL/CLL: Important identified risk Stevens-Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN)

Evidence for linking the risk to the medicine	SJS and TEN 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 important identified risks of GP2013.
Risk factors and risk groups	So far, no specific risk factor for the rituximab induced SJS or TEN has been identified.

Risk minimization measures	Routine risk minimization measures: SmPC section 4.4 and 4.8; section 4.4 where recommendation to discontinue treatment permanently in case of severe skin reactions such as Toxic Epidermal Necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome with a suspected relationship to rituximab is included; section 4.8 PL section 4 Legal status: Prescription only

Table 1-12 NHL/CLL: Important potential risk posterior reversible encephalopathy syndrome (PRES)

Evidence for linking the risk to the medicine	PRES has been described a a selected adverse reaction in section 4.8 Undesirable effects of the SmPC MabThera and is therefore considered as potential risk of GP2013.
Risk factors and risk groups	The syndrome is commonly found to be associated with acute hypertension, preeclampsia or eclampsia, renal disease, sepsis, and exposure to immunosuppressive agents.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.8 PL section 4 Legal status: Prescription only

Table 1-13 NHL/CLL: Important potential risk opportunistic infections

Evidence for linking the risk to the medicine	MabThera should not be administered to patients with opportunistic infections (see section 4.3 of the SmPC MabThera) and is therefore considered as potential risk of GP2013.
Risk factors and risk groups	Opportunistic infections are more common in HIV positive patients with NHL. The risk in these patients to develop *Pneumocystis pneumonia* infections increased with decreasing CD4 positive cell counts.
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 sections 2 and 4 Legal status: Prescription only
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study GP13-301 See section 2.3 of this summary for an overview of the post-authorization development plan.

Table 1-14 NHL/CLL: Important potential risk prolonged B-cell depletion

Evidence for linking the risk to the medicine	As per section 5.1 Pharmacological properties of the SmPC MabThera, a small proportion of patients had prolonged peripheral B-cell depletion lasting 2 years or more after their last dose of MabThera. Prolonged B-cell depletion is therefore considered as potential risk of GP2013.
Risk factors and risk groups	No specific risk factor could be identified predisposing patients to prolonged B-cell depletion.
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.8 and 5.1 PL section 4 Legal status: Prescription only

Table 1-15 CLL only: Important potential risk increased risk of Grade 3/4 serious blood and lymphatic AEs in patients older than 70 years

Evidence for linking the risk to the medicine	An increased risk of Grade 3/4 serious blood and lymphatic adverse events (AEs) in patients >70 years has been described as a selected adverse reaction in section 4.8 Undesirable effects of the SmPC MabThera and is therefore considered as potential risk of GP2013.
Risk factors and risk groups	Factors associated with cytopenia in CLL patients were older age, advanced Rai stage disease, and lower baseline blood counts. Patients with CLL are at special risk due to their impaired immune response resulting from the bone marrow infiltration by the underlying disease and from sequels from myelotoxic treatment.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.8 PL section 4 Legal status: Prescription only

Table 1-16 NHL/CLL: Important potential risk acute myeloid leukemia (AML)/Myelodysplastic syndrome (MDS)

Evidence for linking the risk to the medicine	As per section 4.4 Special warnings and precautions for use of the SmPC MabThera, the risk of MDS/AML cannot be excluded at this time. AML and MDS are therefore considered as potential risks of GP2013.
Risk factors and risk groups	Patients undergoing therapy with alkylating agents, topo-isomerase II-targeted drugs and radiation are at a general increased risk. Individual predisposing factors, including polymorphisms in detoxification and DNA repair enzymes have been identified. Specific risk for development of AML and MDS in patients treated with rituximab could not be identified.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.4 Legal status: Prescription only

Table 1-17 NHL/CLL: Important potential risk second malignancies

Evidence for linking the risk to the medicine	As per section 4.4 Special warnings and precautions for use of the SmPC MabThera, the present data do not seem to suggest any increased risk of malignancy. However, the possible risk for the development of solid tumors cannot be excluded at this time. Second malignancies are therefore considered as potential risks of GP2013.
Risk factors and risk groups	NHL patients have a significant greater risk of developing second malignancies, especially leukemia, myeloma, and neoplasm of the bone and soft tissue, thyroid, central nervous system, skin, stomach, head and neck, liver and biliary tract, and the lungs and mediastinum. Patients ≥60 years, being male, comorbidities of chronic obstructive pulmonary disease, liver cirrhosis, hepatitis C infection and therapy containing radiotherapy have an increased risk.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.4 Legal status: Prescription only

Table 1-18 NHL/CLL: Important potential risk off label use in pediatric patients

Evidence for linking the risk to the medicine	As per SmPC MabThera, a small number of spontaneous and literature cases of hypogammaglobulinemia have been observed in pediatric patients treated with rituximab, in some cases severe and requiring long-term immunoglobulin substitution therapy. The consequences of long term B cell depletion in pediatric patients are unknown. Off-label use in pediatric patients is therefore considered as potential risk of GP2013.
Risk factors and risk groups	Not applicable
Risk minimization measures	Routine risk minimization measures: SmPC section 4.2 PL section 2 Legal status: Prescription only

Table 1-19 NHL/CLL: Important potential risk administration route error

Evidence for linking the risk to the medicine	As per SmPC MabThera, it is important to check the medicinal product labels to ensure that the appropriate formulation (intravenous or subcutaneous formulation) is being given to the patient, as prescribed. Administration route error is therefore considered as potential risk of GP2013.
Risk factors and risk groups	Patients treated for NHL or CLL
Risk minimization measures	Routine risk minimization measures: SmPC section 4.2 PL section 3 The outer carton as well as the vial label of the product states: For intravenous use after dilution. Legal status: Prescription only Additional risk minimization measure: Health care Professional (HCP) alert card

Table 1-20 NHL/CLL: Missing information: Use in pregnancy and lactation

Risk minimization measures	Routine risk minimization measures: SmPC sections 4.6 and 5.3 PL section 2 Legal status: Prescription only

Table 1-21 RA, GPA and MPA: Important identified risk infusion-related reactions

Evidence for linking the risk to the medicine	Infusion-related reactions 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	No specific risk factors have been identified for patients with RA, GPA or MPA.
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.2, 4.4, 4.8 and 5.1; sections 4.2 and 4.4 where recommendations for pre-medication, management of infusion-related reactions and monitoring of patients are given PL section 4; PL section 4 also describes infusion modifications in case of infusion-related reactions Legal status: Prescription only Additional risk minimization measures: HCP educational leaflet
Additional pharmacovigilance activities	Additional pharmacovigilance activities: **RA:** Participation in European registries (BSRBR, ARTIS, RABBIT) See section 2.3 of this summary for an overview of the post-authorization development plan.

Table 1-22 RA, GPA and MPA: 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: **RA:** SmPC sections 4.3, 4.4, 4.5 and 4.8; section 4.4 where recommendation for exercising caution when considering the use of rituximab in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection is included PL sections 2 and 4 Legal status: Prescription only **GPA and MPA:**

	SmPC sections 4.3, 4.4 and 4.8; section 4.4 where recommendation for exercising caution when considering the use of rituximab in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection is included. PL sections 2 and 4 Legal status: Prescription only Additional risk minimization measures: HCP educational leaflet, Patient educational leaflet, Patient alert card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: **RA:** Participation in European registries (BSRBR, ARTIS, RABBIT) See section 2.3 of this summary for an overview of the post-authorization development plan.

Table 1-23 RA, GPA and MPA: Important identified risk impaired immunization response

Evidence for linking the risk to the medicine	Immunisations are listed in section 4.4 Special warnings and precautions for use of the SmPC MabThera and are therefore considered as an important identified risk of GP2013.
Risk factors and risk groups	None identified
Risk minimization measures	Routine risk minimization measures: SmPC section 4.4 which also recommends that patients treated with Rixathon / Riximyo may receive non-live vaccinations, vaccination with live virus vaccines is not recommended; PL section 2 Legal status: Prescription only
Additional pharmacovigilance activities	Additional pharmacovigilance activities: **RA:** Participation in European registries (BSRBR, ARTIS, RABBIT) See section 2.3 of this summary for an overview of the post-authorization development plan.

Table 1-24 RA, GPA and MPA: 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: **RA:** SmPC sections 4.3, 4.4, 4.8 and 5.1; section 4.4 where recommendation for monitoring of patients at regular intervals and suspension of further dosing if PML is suspected, considering further evaluation and permanently discontinuing dosing of Rixathon / Riximyo if a patient develops PML is included

	PL section 4 Legal status: Prescription only **GPA and MPA:** SmPC sections 4.3 and 4.4 where recommendation for monitoring of patients at regular intervals and suspension of further dosing if PML is suspected, considering further evaluation and permanently discontinuing dosing of Rixathon / Riximyo if a patient develops PML is included Legal status: Prescription only Additional risk minimization measures: HCP educational leaflet, Patient educational leaflet, Patient alert card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: **RA:** Participation in European registries (BSRBR, ARTIS, RABBIT) See section 2.3 of this summary for an overview of the post-authorization development plan.

Table 1-25 RA, GPA and MPA: Important identified risk neutropenia (including prolonged)

Evidence for linking the risk to the medicine	Neutropenia is listed in 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	**RA:** The use of rituximab is indicated only in combination with methotrexate. Methotrexate can have a myelosuppressive effect. **GPA and MPA:** Cyclophosphamide, the current standard of care, is well-known to induce neutropenia. Also the concomitant use of high dose glucocorticosteroids can induce neutropenia.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.4 and 4.8; section 4.4 where recommendation for performing regular full blood counts is included; PL section 4 Legal status: Prescription only
Additional pharmacovigilance activities	Additional pharmacovigilance activities: **RA:** Participation in European registries (BSRBR, ARTIS, RABBIT) See section 2.3 of this summary for an overview of the post-authorization development plan.

Table 1-26 RA, GPA and MPA: Important identified risk HBV reactivation

Evidence for linking the risk to the medicine	HBV reactivation 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	The host serological status and HBV-DNA levels are major risk factors for HBV reactivation: HBsAg carriers are at greater risk, and the risk increases with HBVDNA load. The risk may be higher in the event of concomitant methotrexate therapy
Risk minimization measures	Routine risk minimization measures: SmPC section 4.4 and 4.8; section 4.4 where recommendation for HBV screening before initiation of treatment with Rixathon / Riximyo is included; PL sections 2 and 4 Legal status: Prescription only
Additional pharmacovigilance activities	Additional pharmacovigilance activities: **RA:** Participation in European registries (BSRBR, ARTIS, RABBIT) See section 2.3 of this summary for an overview of the post-authorization development plan.

Table 1-27 RA, GPA and MPA: Important identified risk hypogammaglobulinemia

Evidence for linking the risk to the medicine	Hypogammaglobulinemia 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	**RA:** Patients with low immunoglobulin level at baseline had an increased tendency to hypogammaglobulinemia. **GPA and MPA:** No specific risk factor could be identified.
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.4 and 4.8 PL section 4 Legal status: Prescription only

Table 1-28 RA, GPA and MPA: Important identified risk SJS / TEN

Evidence for linking the risk to the medicine	SJS and TEN 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 important identified risks of GP2013.
Risk factors and risk groups	So far, no specific risk factor for the rituximab induced SJS or TEN has been identified.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.4 and 4.8; section 4.4 where recommendation to discontinue treatment permanently in case of severe skin reactions such as Toxic Epidermal Necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome with a suspected relationship to rituximab is included; PL section 4 Legal status: Prescription only

Table 1-29 RA, GPA and MPA: Important potential risk PRES

Evidence for linking the risk to the medicine	PRES has been described a a selected adverse reaction in section 4.8 Undesirable effects of the SmPC MabThera and is therefore considered as potential risk of GP2013.
Risk factors and risk groups	The syndrome is commonly found to be associated with acute hypertension, preeclampsia or eclampsia, renal disease, sepsis, and exposure to immunosuppressive agents.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.8 PL section 4 Legal status: Prescription only
Additional pharmacovigilance activities	Additional pharmacovigilance activities: **RA:** Participation in European registries (BSRBR, ARTIS, RABBIT) See section 2.3 of this summary for an overview of the post-authorization development plan.

Table 1-30 RA, GPA and MPA: Important potential risk opportunistic infections

Evidence for linking the risk to the medicine	MabThera should not be administered to patients with opportunistic infections (see section 4.3 of the SmPC MabThera) and is therefore considered as potential risk of GP2013.
Risk factors and risk groups	**RA:** Chronic pulmonary/heart disease, extra-articular involvement, and low IgG before rituximab treatment were independent risk factors for serious infections. **GPA and MPA:** Risk factors for severe infections in GPA patients are a high cumulative dose of cyclophosphamide, low CD4 cell count and a significant drop in total immunoglobulins after the first rituximab round.
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.3, 4.4, 4.5 and 4.8; section 4.4 where recommendation for exercising caution when considering the use of rituximab in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection is included PL sections 2 and 4 Legal status: Prescription only
Additional pharmacovigilance activities	Additional pharmacovigilance activities: **RA:** Participation in European registries (BSRBR, ARTIS, RABBIT) See section 2.3 of this summary for an overview of the post-authorization development plan.

Table 1-31 RA, GPA and MPA: Important potential risk malignant events

Evidence for linking the risk to the medicine	As per SmPC MabThera, the possible risk for the development of solid tumors cannot be excluded at this time. Malignent events are therefore considered as potential risk of GP2013.

Risk factors and risk groups	**RA:** It is thought that ongoing immunologic stimulation over time may increase the risk of malignant transformation of immune system cells and decrease the number of T-suppressor lymphocytes, thus increasing rates of lymphoma malignancy in patients with RA. Overall, the risk of malignancy among patients with RA may be due in part to the autoimmune pathogenesis of RA and common etiology between RA and malignancy, including genetic factors, smoking-related tissue necrosis and viral infection. The use of immunomodulatory therapy, such as DMARDs, that may alter normal immunosurveillance and elevate the risk of malignancy. **GPA and MPA:** Men had a slightly higher risk to develop a malignancy than women. The use of immune inhibitors, etanercept and cyclophosphamide increased the risk. Also the dysfunction in immune system may raise the cancer risk. The longstanding immune activation in patients with ANCA-associated vasculitis may be oncogenic.
Risk minimization measures	Routine risk minimization measures: **RA:** SmPC sections 4.4 and 5.1 Legal status: Prescription only **GPA and MPA:** SmPC section 4.8 Legal status: Prescription only
Additional pharmacovigilance activities	Additional pharmacovigilance activities: **RA:** Participation in European registries (BSRBR, ARTIS, RABBIT) See section 2.3 of this summary for an overview of the post-authorization development plan.

Table 1-32 RA, GPA and MPA: Important potential risk impact on cardiovascular disease

Evidence for linking the risk to the medicine	As per SmPC MabThera, patients with pre-existing cardiac conditions and those who experienced prior cardiopulmonary adverse reactions should be closely monitored. Additionally, various cardiac disorders have have occurred in patients treated with MabThera. The impact on cardiovascular disease is therefore considered as potential risk of GP2013.
Risk factors and risk groups	No specific factor predisposing RA, GPA and MPA patients with a cardiovascular history for an impact on their cardiovascular disease could be identified apart from the risk factors applicable in the non-target population as well.
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.2, 4.3, 4.4 and 4.8 PL sections 2 and 4 Legal status: Prescription only
Additional pharmacovigilance activities	Additional pharmacovigilance activities: **RA:** Participation in European registries (BSRBR, ARTIS, RABBIT)

	See section 2.3 of this summary for an overview of the post-authorization development plan.

Table 1-33 RA, GPA and MPA: Important potential risk gastointestinal perforation

Evidence for linking the risk to the medicine	Gastrointestinal perforation perforation is listed for patients with NHL or CLL in section 4.8 Undesirable effects of the SmPC MabThera and is therefore considered as an important potential risk of GP2013 for the treatment of RA, GPA or MPA.
Risk factors and risk groups	No specific factor predisposing RA, GPA and MPA patients with a cardiovascular history for an impact on their cardiovascular disease could be identified apart from the risk factors applicable in the non-target population as well.
Risk minimization measures	Routine risk minimization measures: Legal status: Prescription only
Additional pharmacovigilance activities	Additional pharmacovigilance activities: **RA:** Participation in European registries (BSRBR, ARTIS, RABBIT) See section 2.3 of this summary for an overview of the post-authorization development plan.

Table 1-34 RA, GPA and MPA: Important potential risk prolonged B-cell depletion

Evidence for linking the risk to the medicine	As per section 5.1 Pharmacological properties of the SmPC MabThera, a small proportion of patients had prolonged peripheral B-cell depletion lasting 2 years or more after their last dose of MabThera. Prolonged B-cell depletion is therefore considered as potential risk of GP2013.
Risk factors and risk groups	No specific risk factor could be identified predisposing patients to prolonged B-cell depletion.
Risk minimization measures	Routine risk minimization measures: **RA:** SmPC sections 4.8 and 5.1 PL section 4 Legal status: Prescription only **GPA and MPA:** SmPC section 5.1 PL section 4 Legal status: Prescription only
Additional pharmacovigilance activities	Additional pharmacovigilance activities: **RA:** Participation in European registries (BSRBR, ARTIS, RABBIT) See section 2.3 of this summary for an overview of the post-authorization development plan.

Table 1-35 RA, GPA and MPA: Important potential risk off-label use in autoimmune disease

Evidence for linking the risk to the medicine	Off-label use in autoimmune diseases has been described for MabThera in section 4.8 Undesirable effects of the SmPC MabThera. Off-label use in autoimmune disease is therefore considered as potential risk of GP2013.
Risk factors and risk groups	Not applicable
Risk minimization measures	Routine risk minimization measures: SmPC section 4.8 Legal status: Prescription only

Table 1-36 RA, GPA and MPA: Important potential risk off label use in pediatric patients

Evidence for linking the risk to the medicine	As per SmPC MabThera, a small number of spontaneous and literature cases of hypogammaglobulinemia have been observed in pediatric patients treated with MabThera, in some cases severe and requiring long-term immunoglobulin substitution therapy. The consequences of long term B cell depletion in pediatric patients are unknown. Off-label use in pediatric patients is therefore considered as potential risk of GP2013.
Risk factors and risk groups	Not applicable
Risk minimization measures	Routine risk minimization measures: **RA:** SmPC section 4.2 PL section 2 Legal status: Prescription only **GPA and MPA:** SmPC sections 4.1 and 4.2 PL section 2 Legal status: Prescription only

Table 1-37 GPA and MPA: Important potential risk relapses

Evidence for linking the risk to the medicine	Relapses have been observed in patients with GPA or MPA (SmPC MabThera) and are therefore considered as potential risk of GP2013.
Risk factors and risk groups	No specific risk factor could be identified predisposing patients to relapse following treatment with a rituximab containing regimen.
Risk minimization measures	Routine risk minimization measures: Legal status: Prescription only

Table 1-38 RA, GPA and MPA: Missing information: Use in pregnancy and lactation

Risk minimization measures	Routine risk minimization measures: SmPC sections 4.6 and 5.3 PL section 2 Legal status: Prescription only

Table 1-39 RA, GPA and MPA: Missing information: Immunogenicity and autoimmune disease

Risk minimization measures	Routine risk minimization measures: SmPC sections 4.5 and 5.1 Legal status: Prescription only

Table 1-40 GPA and MPA: Missing information: Long-term use in GPA/MPA patients

Risk minimization measures	Routine risk minimization measures: Legal status: Prescription only

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

1.2.3.1 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.

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

Table 1-41 Other studies in the post-authorization development plan

Study short name	Rationale and study objectives
Clinical study GP13-301 Clinical study in patients with previously untreated, advanced stage follicular lymphoma	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 Primary objective: To demonstrate comparability of the overall response rate (ORR) Safety objective: - Safety of GP2013 in comparison to MabThera® either as single agent or in combination with CVP; - Addressing safety concerns: Infusion related reactions, infections (including serious infections), serious viral infections, neutropenia (including prolonged neutropenia), opportunistic infections. - Incidence of immunogenicity (anti-drug antibody formation)
Register BSRBR - British Society of Rheumatology Biologics Register	To compare the risk of development over at least 5 years, of serious infections, malignancy and other specified outcomes (such as myocardial infarction) between a recruited group of patients with rheumatoid arthritis who are recipients of Rixathon and reference cohorts of patients with similar disease characteristics but who are exposed to established anti-TNF agents Primary objective: To test that Rixathon in patients with rheumatoid arthritis is associated with a similar risk of developing serious infections compared to patients with similar disease activity receiving established anti-TNF drugs

Study short name	Rationale and study objectives
Register ARTIS - Anti Rheumatic Therapy in Sweden	Nation-wide safety monitoring of Rixathon treatment in patients with rheumatic diseases in Sweden Primary objective: To provide long term safety data on the use of Rixathon in Sweden for rheumatoid arthritis
Register Rabbit - Rheumatoide Arthritis: Beobachtung der Biologika-Therapie, German registry	RABBIT is an independent long-term observational cohort study of the safety and effectiveness of Rixathon in rheumatoid arthritis Primary objective: To study the long-term safety To describe the long-term effectiveness of treatment To describe selected direct and indirect costs of therapy