Summary of Risk Management Plan for Truxima®

Active substance:	Rituximab
Dosage strength:	10mg/ml
Pharmaceutical form:	Concentration for solution for infusion
Version number of RMP summary	2.0
Name of Marketing Authorisation Holder:	iQone Healthcare Switzerland SA
Date:	26 January 2021
Reference RMP	EU RMP version 11.0 (CHMP positive opinion dated 29 October 2020)

Disclaimer:

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 minimise them.
The RMP summary of Truxima® 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.
Please note that the reference document which is valid and relevant for the effective and safe use of Truxima® in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. iQone Healthcare Switzerland SA is fully responsible for the accuracy and correctness of the content of the published summary RMP of Truxima®.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Truxima/Blitzima/Ritemvia (Rituximab)

This is a summary of the risk management plan (RMP) for Truxima/Blitzima/Ritemvia. The RMP details important risks of Truxima/Blitzima/Ritemvia, how these risks can be minimised, and how more information will be obtained about Truxima/Blitzima/Ritemvia's risks and uncertainties (missing information).

Truxima/Blitzima/Ritemvia's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Truxima/Blitzima/Ritemvia should be used.

This summary of the RMP for Truxima/Blitzima/Ritemvia 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 Truxima/Blitzima/Ritemvia's RMP.

I. The medicine and what it is used for

Truxima is authorised for Non-Hodgkin's Lymphoma, Chronic Lymphocytic Leukaemia, Rheumatoid Arthritis, Granulomatosis with Polyangiitis and Microscopic Polyangiitis, and Pemphigus Vulgaris; Blitzima is authorised for Non-Hodgkin's Lymphoma, Chronic Lymphocytic Leukaemia, Granulomatosis with Polyangiitis and Microscopic Polyangiitis, and Pemphigus Vulgaris; and Ritemvia is authorised for Non-Hodgkin's Lymphoma, Granulomatosis with Polyangiitis and Microscopic Polyangiitis, and Pemphigus Vulgaris (see SmPCs for the full indication). It contains rituximab as the active substance and it is given by intravenous (IV) infusion.

Further information about the evaluation of Truxima/Blitzima/Ritemvia's benefits can be found in Truxima/Blitzima/Ritemvia's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

Truxima

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

Blitzima

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

Ritemvia

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

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Truxima/Blitzima/Ritemvia, together with measures to minimise such risks and the proposed studies for learning more about Truxima/Blitzima/Ritemvia's risks, are outlined below.

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

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

Together, these measures constitute routine risk minimisation measures.

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

- Infections including serious infections
- Progressive multifocal leukoencephalopathy
- Administration route error

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 Truxima/Blitzima/Ritemvia is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Truxima/Blitzima/Ritemvia are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Truxima/Blitzima/Ritemvia. 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);

List of important risks and missing information	
Important identified risks	Infections including serious infections (all indications) Progressive multifocal leukoencephalopathy (PML) (all indications) Hepatitis B virus (HBV) reactivation (all indications) Hypogammaglobulinaemia (Non-oncology indications)
Important potential risks	Malignancy (Non-oncology indications) Impact on cardiovascular disease (Non-oncology indications) Relapse of GPA/MPA (GPA/MPA only) Administration route error (NHL/CLL)
Missing information	Use during pregnancy or lactation (all indications) Long-term use in GPA/MPA patients (GPA/MPA)

II.B Summary of important risks

Important Identified Risk- Infections including serious infections (all indications)	
Evidence for linking the risk to the medicine	It is not possible to make meaningful generalisations about the background incidence and prevalence of infections as these vary with time, location, the nature of the infection, and the susceptibility of the population exposed to risk, even within the EU.
Risk factors and risk groups	• Very young people and elderly people • Poor nutritional status • immunosuppressive medications (such as transplant recipients), including steroids • haematological malignancy • treatment with chemotherapy drugs or radiation • splenectomy • longstanding diabetes, HIV/AIDS, or cirrhosis • large burns or severe trauma
Risk minimisation measures	<u>Routine risk minimisation measures</u> SmPC section 4.2 SmPC section 4.3 SmPC section 4.4 SmPC section 4.8 Legal status: Restricted medical prescription <u>Additional risk minimisation measures:</u> Non-oncology indications only - Guide for healthcare professionals - Patient guide - Patient alert card
Additional pharmacovigilance activities	None

Important Identified Risk- Progressive multifocal leukoencephalopathy (PML) (all indications)

Evidence for linking the risk to the medicine	PML is most frequently diagnosed in patients infected with HIV. Incidence rates in HIV-infected patients treated with antiretroviral therapy have been reported to be 0.06% in Switzerland, and 1.3 cases per 1,000 person-years in Denmark (Amend *et al.* 2010). Incidence rates estimated from a retrospective observational cohort derived from a large US health insurer database have been published for PML in patients without HIV for the period January 2000 to June 2008 (Amend *et al*. 2010). There were 138,469 patients with autoimmune diseases, 25,706 with NHL or CLL, and 8,778 with transplants. Among 699 people who met screening criteria for potential PML, 89 had a diagnosis of PML. Medical records were sought for 24 patients without HIV, and six had confirmed PML upon review of medical records. The PML incidence rate was 2.4 (95% confidence interval [CI] 0.06–13.18) in the systemic lupus erythematosus cohort and 10.8 (95% CI 0.27–60.39) in the autoimmune vasculitis cohort per 100,000 person-years; this rate estimate was based on one case reported in a patient with Wegener's granulomatosis (GPA). In the NHL and CLL cohorts, the incidence rate was 8.3 (95% CI 1.71–24.24) and 11.1 (95% CI 0.28–61.74) per 100,000 person-years. The incidence rate among patients with bone marrow transplantation was 35.4 per 100,000 person-years (95% CI 0.90–197.29). There were no cases of PML among patients with rheumatoid arthritis (95% CI 0.0–2.24), multiple sclerosis (95% CI 0.0–5.24), Sjögren's disease (95% CI 0.0–21.84), or solid organ transplantation (95% CI 0.0–26.81). In an estimate derived from a hospital discharge sample in the USA (20% of hospitalisations), the cumulative incidence of PML in rheumatoid arthritis was 1 per 100,000 admissions (Molloy ES *et al*. 2008). When patients with defined risk factors for PML were excluded, the incidence of PML in rheumatoid arthritis patients was 0.4 per 100,000 admissions. There are a number of case reports of PML in the global literature in patients with GPA/MPA. In a review covering the years 1992 to 2010 there were five published reports of PML in patients with GPA, none of whom had been treated with rituximab (Ettinger J *et al.* 1989; Choy DS *et al.* 1992; Morgenstern LB *et al.* 1995; Pagnoux C *et al.* 2003; Wang Y *et al.* 2004). All five patients had received cyclosporin and prednisone. Studies reporting the incidence of PML among patients with haematological malignancies are limited. Carson *et al.* (2009) referred to a small number of studies assessing the incidence of PML namely, one population-based study that estimated an incidence of PML of 0.07% based on three cases of PML identified in HIV-negative patients with haematological malignancies over 11 years in Manitoba, Canada (Power *et al.* 2000). A higher incidence of PML of

	0.52% was reported in another study in patients with CLL; these patients were treated with fludarabine (Gonzales *et al.* 1999). Carson *et al.* (2009a) concluded that estimating the risk of PML attributable to the underlying malignancy as opposed to immunosuppression due to treatment was complicated by the rarity of the disease and few large trials from which incidences can be determined prospectively. Fludarabine was seen as the drug most closely associated with PML possibly due to the effect of T-cell depletion (Garcia-Suarez *et al.* 2005). Carson *et al.* (2009) also reported that it is not possible accurately to estimate the incidence of PML associated with rituximab among persons with haematological malignancies because of incomplete reporting of PML cases and incomplete data on the number of unique patients with lymphoid malignancies who have received rituximab. It has also been emphasised that the epidemiology of PML in the setting of lymphoid malignancies has changed in recent years; before 1990, most PML cases occurred in Hodgkin's disease. Whereas in recent years, with the development of purine analogues, haematopoietic stem cell transplantation, and rituximab, most PML cases occur in non-HIV-infected persons with NHL or CLL (Garcia-Suarez *et al.* 2005). As rituximab is routinely added to the treatment for haematological malignancies, the contribution of confounding factors to the development of a rare disease such as PML is difficult to estimate. Bower *et al.*(1997) reviewed B-cell CLL patients seen at the Mayo Clinic from 1987 to 1991 for neurological complications including PML. Among 962 CLL patients there were five cases of PML (0.5%) and three further unconfirmed cases. The incidence rate of confirmed PML was estimated to be 108.5 per 100,000 patient-years (95% CI 35.2-253.1 per 100,000 patient-years). The authors noted that their study may overestimate the incidence of PML in the general CLL population as the Mayo Clinic is a tertiary care centre, and therefore only receives more severe patients. A single-centre study from Italy reported the incidence of PML amongst 976 subjects with NHL diagnosed between 1994 and 2008 (Tuccori *et al.* 2010). No case of PML was identified amongst 459 subjects that had not been treated with rituximab (Incidence Rate [IR] 0 per 100,000 person-years, 95% CI 0-180). There were five reports of PML among 517 subjects with NHL treated with rituximab (IR 240 0 per 100,000 person-years, 95% CI 100-560). The incidence rates should be interpreted with caution due to possible detection bias due to the use of historical controls, and the effect of publicity concerning the association between PML and rituximab treatment.
Risk factors and risk groups	• HIV/AIDS (especially with CD4+ lymphocyte counts less than 200 cells/µL)

	• immunosuppressive medications (such as haematopoietic/solid organ transplant recipients), including steroids • haematological malignancies • treatment with chemotherapy drugs (especially fludarabine) • treatment with natalizumab or efalizumab • autoimmune disorders • tuberculosis
Risk minimisation measures	<u>Routine risk minimisation measures</u> SmPC section 4.4 SmPC section 4.8 Legal status: Restricted medical prescription <u>Additional risk minimisation measures:</u> Non-oncology indications only - Guide for healthcare professionals - Patient guide - Patient alert card
Additional pharmacovigilance activities	None

Important Identified Risk- Hepatitis B virus (HBV) reactivation (all indications)	
Evidence for linking the risk to the medicine	Data have been published that allow one to estimate HBV reactivation rates amongst patients with rheumatoid arthritis who have been treated with TNF-inhibitors (the rheumatoid arthritis population most likely to receive rituximab). In a study of 88 HBcAb-positive patients, 18 (20.5%) patients were HBsAg-positive, 12 (13.6%) patients were HBsAg-negative/HBsAb-negative and 58 (65.9%) patients were HBsAg-negative/HBsAb-positive before starting anti-TNFα therapy. Among HBsAg-positive patients receiving anti-TNFα therapy, HBV reactivation was documented in none of 10 patients who received lamivudine pre-emptive therapy. In contrast, five (62.5%) of eight patients without antiviral prophylaxis developed HBV reactivation (Lan *et al.* 2011). In another study of 50 patients with RA who had antibodies against hepatitis B core antigen and who had started treatment with disease-modifying antirheumatic drugs, including tumour necrosis factor inhibitors. HBV DNA levels were measured every 2–3 months. The

	mean observation period was 23 months (range 12–32 months). HBV reactivation occurred in 2 of 5 patients with HBV surface antigen (HBsAg) and in 1 of 45 patients without HBsAg. In patients who received anti-TNFα therapy, antibodies against HBsAg decreased significantly (Tamori *et al.* 2011).
Risk factors and risk groups	Patients with chronic inactive HBV are at risk.
Risk minimisation measures	Routine risk minimisation measures SmPC section 4.3 SmPC section 4.4 SmPC section 4.8 Legal status: Restricted medical prescription Additional risk minimisation measures: No additional risk minimisation measures
Additional pharmacovigilance activities	None

Important Identified Risk- Hypogammaglobulinaemia (Non-oncology indications)	
Evidence for linking the risk to the medicine	Estimates of the incidence/prevalence of hypogammaglobulinaemia in untreated patient populations with RA or GPA/MPA are not available.
Risk factors and risk groups	Male gender, kidney involvement and a 1000 mg biannual treatment regimen have been shown to increase the risk of discontinuation of rituximab treatment for granulomatosis with polyangiitis due to hypogammaglobulinaemia (Besada *et al*. 2014).
Risk minimisation measures	Routine risk minimisation measures SmPC section 4.3 SmPC section 4.4 SmPC section 4.8 Legal status: Restricted medical prescription Additional risk minimisation measures: No additional risk minimisation measures
Additional pharmacovigilance activities	None

Important Potential Risk- Malignancy (Non-oncology indications)	
Evidence for linking the risk to the medicine	It is not possible to make meaningful generalisations about the background incidence and prevalence of malignancies as these vary with time, location, behavioural factors, nutritional and social factors, and the nature of the malignancy, even within the EU.
Risk factors and risk groups	Risk factors for malignancy will vary significantly depending on the malignancy.
Risk minimisation measures	<u>Routine risk minimisation measures</u> SmPC section 4.4 SmPC section 4.8 Legal status: Restricted medical prescription <u>Additional risk minimisation measures:</u> No additional risk minimisation measures
Additional pharmacovigilance activities	None

Important Potential Risk- Impact on cardiovascular disease (Non-oncology indications)	
Evidence for linking the risk to the medicine	A small number of studies have estimated the relative risk of cardiovascular events in general (as opposed to specific cardiovascular events such as infarction or stroke) in subjects with rheumatoid arthritis compared to the general population and confirm that the risk is greater in the rheumatoid population. These studies also provide estimates of incidence of cardiovascular disease in the rheumatoid population that has not been exposed to rituximab to any significant extent. It is difficult directly to compare these studies due to differences in rheumatoid arthritis definition, study design, patient population, disease duration, and length of follow-up. One study examined 25,385 adults who had at least three diagnoses for rheumatoid arthritis during the study period. During the 5-year study period, 375 patients with rheumatoid arthritis had a hospital admission for myocardial infarction, 363 had a hospitalisation for stroke, 437 died from cardiovascular causes and 1042 had one of these outcomes. The crude incidence rate for cardiovascular events was 14.8 per 1000 person-years (Solomon *et al.* 2006). In another study 236 consecutive patients with rheumatoid arthritis were assessed for the one-year occurrence of 1) cardiovascular-related hospitalisations, including myocardial infarction, stroke or other arterial occlusive events, or arterial revascularisation

	procedures, or 2) cardiovascular deaths. Of the 236 patients, 234 were observed for 252 patient-years, during which 15 cardiovascular events occurred. Of these, 7 incident events occurred during the 204 patient-years contributed by patient age range of 25–65 years, for an incidence of 3.43 per 100 patient-years (Rincon del *et al.* 2001). Another study examined all-cause mortality rates and the incidence of major vascular events among patients with rheumatoid arthritis (RA), osteoarthritis without RA, or no arthritis using the UK General Practice Research Database. A retrospective cohort of patients 2.37 million patients (1.11 million men and 1.26 million women) 40 years and older was followed until the earliest of death, disenrollment, or the occurrence of an incident vascular event. Over a mean duration of follow-up of almost 5 years, the standardised incidence rates for all vascular events were 17.6 per 1000 patient-years for men with RA, and 12.6 per 1000 patient-years for women (Watson *et al.* 2003). There are fewer published data on the background risk for cardiovascular events in subjects with systemic vasculitis. No publications have been found that provide estimates of incidence or prevalence for cardiovascular events in general in the systemic vasculitis population that has not been exposed to rituximab, although the relative risk of cardiovascular mortality and morbidity has been shown to higher in subjects with systemic vasculitis than in the general population (Faurschou *et al.* 2009).
Risk factors and risk groups	Risk factors for increased cardiovascular mortality and morbidity in subjects with rheumatoid arthritis or systemic vasculitis exposed to rituximab have not been identified.
Risk minimisation measures	<u>Routine risk minimisation measures</u> SmPC section 4.3 SmPC section 4.4 SmPC section 4.8 Legal status: Restricted medical prescription <u>Additional risk minimisation measures:</u> No additional risk minimisation measures
Additional pharmacovigilance activities	None

Important Potential Risk- Relapse of GPA/MPA (GPA/MPA only)	
Evidence for linking the risk to the medicine	The safety concern appears to derive from the results of the RAVE study submitted at the time of marketing authorisation application for

	the extension of the indication of MabThera® to include granulomatosis with polyangiitis and microscopic polyangiitis (MabThera® EPAR). The RAVE study was a randomised, double-blind, non-inferiority, multi-centre parallel-group study comparing intravenous rituximab with oral cyclosporin for the treatment of ANCA-associated vasculitis. The observation period was 18 months. Remission was induced during the first 6 months of treatment with either rituximab or cyclosporin. Thereafter, patients were treated with either azathioprine or placebo for 12 months. Patients who relapsed during the 12-month maintenance phase of the study were treated with rituximab to maintain remission. Time-to-flare analyses indicated that the proportions of patients who remained in complete remission were comparable up to 12 months after randomisation. After 12 months, the proportion of patients remaining in complete remission was numerically lower in the rituximab group than in the cyclosporin group. More severe flares occurred between 12 and 18 months in the rituximab than cyclosporin group (8 vs. 4). Between 6 and 18 months, more limited (i.e. less severe) flares also occurred in the rituximab than cyclosporin group (24 vs. 16).
Risk factors and risk groups	Not known
Risk minimisation measures	Routine risk minimisation measures SmPC section 5.1 Legal status: Restricted medical prescription Additional risk minimisation measures: No additional risk minimisation measures
Additional pharmacovigilance activities	None

Important Potential Risk- Administration route error (NHL/CLL)	
Evidence for linking the risk to the medicine	The administration route error for an IV formulation being administered by the SC route has not been reported. In MabThera, systemic exposure to rHuPH20 in humans may occur after accidental IV administration of the rituximab SC formulation. Embryofetal toxicity resulting from systemic exposure to rHuPH20 maybe observed after intravenous administration of the SC formulation (MabThera® RMP v19.1)

Risk factors and risk groups	Not known
Risk minimisation measures	Routine risk minimisation measures SmPC section 4.2 Legal status: Restricted medical prescription Additional risk minimisation measures: NHL/CLL patients only - Physician information
Additional pharmacovigilance activities	None

Missing information - Use during pregnancy or lactation (all indications)	
Risk minimisation measures	Routine risk minimisation measures SmPC section 4.6 Legal status: Restricted medical prescription Additional risk minimisation measures: No additional risk minimisation measures
Additional pharmacovigilance activities	None

Missing information - Long-term use in GPA/MPA patients (GPA/MPA)	
Risk minimisation measures	Routine risk minimisation measures Legal status: Restricted medical prescription Additional risk minimisation measures: No additional risk minimisation measures
Additional pharmacovigilance activities	None

II.C Post-authorisation development plan

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

There are no studies which are conditions of the marketing authorisation or specific obligation of Truxima/Blitzima/Ritemvia.

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

There are no studies required for Truxma/Blitzima/Ritemvia.