PUBLIC SUMMARY OF THE RISK MANAGEMENT PLAN

RUXIENCE (RITUXIMAB)

Marketing Authorization Number 67952

Ruxience 100 mg/10 ml concentrate for solution for infusion

Ruxience 500 mg/50 ml concentrate for solution for infusion

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LIST OF ABBREVIATIONS

Abbreviation	Term
ALL	Acute lymphoblastic leukaemia
AAV	Anti-neutrophil cytoplasmic antibody associated vasculitis
ANCA	Anti-neutrophil cytoplasmic antibody
ARTIS	Anti-Rheumatic Therapy in Sweden registry
BSRBR	British Society of Rheumatology Biologics Register
CD4+	Cluster of differentiation 4 positive
CI	Confidence interval
CCS/ eGPA	Churg-Strauss Syndrome
CLL	Chronic lymphocytic leukaemia.
CMV	Cytomegalovirus
CNS	Central nervous system
CVD	Cardiovascular disorders
DMARDs	Disease-modifying anti-rheumatic drugs
EM	extensive metabolizer
EMA	European Medicines Agency
EPAR	European Public Assessment Reports
EU	European Union
EUVAS	European Vasculitis Study Group
GPA	Granulomatosis with polyangiitis
HACA	Human Anti-Chimeric Antibody
HCP	Health care professional
HBV	Hepatitis B virus
HIV	Human immunodeficiency virus
IgG1	Immunoglobulin G1
ITP	Idiopathic thrombocytopoenic purpura
IV	intravenous
KD	Kawasaki disease
LN	Lupus nephritis
MPA	microscopic polyangiitis
MS	Multiple sclerosis
NHL	Non-Hodgkin's lymphoma
NMSC	Nonmelanoma skin cancer
PAC	Patient alert card
PL	Package leaflet
PML	Progressive multifocal leukoencephalopathy
PI	Package insert
RA	rheumatoid arthritis
RABBIT	Rheumatoid Arthritis-Observation of Biologic Therapy
RMP	Risk management plan
RP	Reference product
SC	subcutaneous
SmPC	Summary of Product Characteristics
SLE	Systemic lupus erythematosus
SMR	Standardized mortality ratio
TNF	tumor necrosis factor
TNFi	tumor necrosis factor inhibitor
TTP	Thrombotic thrombocytopoenic purpura

Abbreviation	Term
US	United States
USA	United States of America

OVERVIEW

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 Ruxience 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 marketing authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Ruxience in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorised by Swissmedic. Pfizer AG is fully responsible for the accuracy and correctness of the content of the published RMP summary of Ruxience.

SUMMARY OF RISK MANAGEMENT PLAN FOR RUXIENCE (RITUXIMAB)

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

Ruxience summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Ruxience should be used.

This summary of the RMP for Ruxience 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 Ruxience's RMP.

I. The Medicine and What It Is Used For

Ruxience proposed indications are: rheumatoid arthritis (RA), granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), Pemphigus vulgaris, Non-Hodgkin's Lymphoma (NHL), and chronic lymphocytic leukaemia (CLL). It contains rituximab as the active substance, and it is given by intravenous (IV) route of administration.

Further information about the evaluation of Ruxience benefits will be found in Ruxience European public assessment report (EPAR), including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Ruxience, together with measures to minimise such risks and the proposed studies for learning more about Ruxience 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 (eg, with or without prescription) can help to minimise its risks.

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

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

In addition to these measures, information about adverse reactions will be collected continuously and regularly analysed, including periodic safety update report (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 Ruxience is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of Ruxience 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 rituximab. 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 (eg, on the long-term use of the medicine).

Table 1. List of important risks and missing information

Important identified risks	• Infusion related reactions (All Indications) • Infections, including serious infections (All Indications) • Progressive multifocal leukoencephalopathy (All Indications) • Hepatitis B reactivation (All Indications) • Hypogammaglobulinaemia (Non-oncology indications)
Important potential risks	• Malignant events (Non-oncology indications) • Impact on cardiovascular disease (Non-oncology indications) • Relapses (GPA/MPA only) • Off-label use in paediatric patients (All Indications) • Administration route error (NHL/CLL)
Missing information	• Use in pregnancy and lactation (All Indications) • Long-term use in GPA/MPA patients (GPA/MPA only)

CLL = chronic lymphocytic leukaemia; GPA = granulomatosis with polyangiitis; MPA = microscopic polyangiitis; NHL = Non-Hodgkin's Lymphoma.

II.B. Summary of Important Risks

Table 2. Important Identified Risk: Infusion related reactions (All Indications)

Evidence for linking the risk to the medicine	Ruxience (rituximab) is a biosimilar medicinal product and the reference product (RP) is MabThera. The evidence of the above-mentioned risk is derived from the Ruxience and MabThera clinical trial data, and the MabThera RMP which provides sufficient evidence from multiple sources (literature, clinical and/or post marketing).

Table 2. Important Identified Risk: Infusion related reactions (All Indications)

Risk factors and risk groups	**RA** Patients who have failed anti-tumour necrosis factor therapy with infliximab, another murine chimeric immunoglobulin G1 (IgG1) antibody, could potentially have developed Human Anti-Chimeric Antibody (HACA) to infliximab, which could cross-react and bind to murine epitopes on rituximab. Such cross-reactive HACA could theoretically increase the risk of an acute infusion related reaction to rituximab, by initiating an allergic or hypersensitivity reaction. **GPA/MPA** None identified. **Pemphigus vulgaris** None identified. **NHL/CLL** Patients with a high tumour burden or with a high number ($\geq 25 \times 10^9$/L) of circulating malignant cells may be at higher risk of severe cytokine release syndrome/infusion-related reactions. These patients should only be treated with extreme caution and when other therapeutic alternatives have been exhausted. These patients should be very closely monitored throughout the first infusion. Consideration should be given to the use of a reduced infusion rate for the first infusion in these patients. Patients with a history of pulmonary insufficiency or those with pulmonary tumour infiltration may be at greater risk of poor outcome and should be treated with increased caution.
Risk minimisation measures	<u>Routine risk minimisation measures</u> European Union (EU) SmPC Section 4.4 *Special warnings and precautions for use* EU SmPC Section 4.8 *Undesirable effects* Package leaflet (PL) Section 4 *Possible side effects* *Medicine's legal status:* Medicinal product subject to restricted medical prescription. <u>Additional risk minimisation measures</u> None.

Table 3. Important Identified Risk: Infections, including serious infections (All Indications)

Evidence for linking the risk to the medicine	Ruxience (rituximab) is a biosimilar medicinal product and the RP is MabThera. The evidence of the above-mentioned risk is derived from the Ruxience and MabThera clinical trial data, and the MabThera RMP which provides sufficient evidence from multiple sources (literature, clinical and/or post marketing).

Table 3. Important Identified Risk: Infections, including serious infections (All Indications)

Risk factors and risk groups	**RA and GPA/MPA** Patients with advanced RA are at a higher risk of infection than the general population largely because of altered immunological function or other factors such as decreased mobility, or therapies used to treat the underlying disease (steroids, immunomodulating agents).[1] A retrospective cohort study found that the rate of infection in RA patients was higher than in patients without RA in each of the 11 infection categories examined; sites associated with the highest relative risk were joints, bone, skin and soft tissues.[1] The hazard ratio for the development of objectively confirmed infections in RA patients compared with non-RA patients, after adjustment for confounding variables, was 1.70. Within RA patients, increasing age, presence of extra-articular manifestations of RA, and co-morbidities, as well as use of corticosteroids, were strong predictors of infection risk. The predicting co-morbidities were chronic lung disease, chronic kidney disease, alcoholism, organic brain disease, and diabetes mellitus. Of the disease-modifying therapies examined, corticosteroids consistently increased infection risk. In large studies, infection rates are clearly increased with cyclophosphamide or azathioprine, whereas methotrexate appears to be associated with minimal, if any, increased infection risk[1]. Data about other disease-modifying anti-rheumatic drugs (DMARDs) are scarce, and the main cause of therapy withdrawal is related to toxicity rather than infection.[2] Anti-tumour necrosis factor-α (TNF-α) agents like infliximab are associated with an increased risk for tuberculosis, hepatitis B virus (HBV) reactivation and opportunistic infections.[3] Risk factors for infection in GPA/MPA patients include the concomitant use of high dose corticosteroids and/or other immunomodulatory agents. **Pemphigus vulgaris** None identified. **NHL/CLL** No risk factors or risk groups have been identified specifically for rituximab and the risk of infection is closely related to concomitant chemotherapy and the patient's underlying condition. In a retrospective analysis,[4] a higher infection rate in NHL patients was associated with granulocytopenia and post splenectomy. The commonest sites of infection were lung, skin, and alimentary canal. Risk factors for infections identified in the literature in patients with CLL include advanced disease stage, previous antineoplastic therapy, refractoriness to fludarabine-based therapy, high serum β_2-microglobulin level, low serum albumin level, low granulocyte count, and high serum creatinine concentration.[5] The risk of serious viral infection/reactivation is mainly related to concomitant chemotherapy and the patient's underlying condition. Fludarabine, in particular, has been associated with an increased risk of serious viral infections including cytomegalovirus (CMV) and John Cunningham (virus)/PML, and this is probably related to the induction of profound cluster of differentiation 4 positive (CD4+) lymphopenia. The risk of developing *Pneumocystis jiroveci* pneumonia among human immunodeficiency virus (HIV) patients rises markedly when circulating CD4+ cell counts fall below 200/μL. A low CD4+ count is likely to be a major risk factor for opportunistic infections in other patients including those receiving immunosuppressive therapy (particularly glucocorticoids) for haematological malignancies such as NHL or CLL. Patients with CLL are predisposed to common as well as opportunistic infections as a result of a number of disease-related factors including immunoglobulin deficiency, abnormal T-cell function, and neutropenia resulting from infiltration of the bone marrow.

Table 3. Important Identified Risk: Infections, including serious infections (All Indications)

Risk minimisation measures	Routine risk minimisation measures EU SmPC Section 4.4 *Special warnings and precautions for use* EU SmPC Section 4.8 *Undesirable effects* PL Section 2 *Warnings and precautions* PL Section 4 *Possible side effects* *Medicine's legal status:* Medicinal product subject to restricted medical prescription. Additional risk minimisation measures (Non-oncology indications) Patient Alert Card (PAC) and educational material for patients and health care professionals (HCPs). The text of the PAC is included in the Package insert (PI) Annexes.

1. McLean-Tooke A, Aldridge C, Waugh S, et al. Methotrexate, rheumatoid arthritis and infection risk: what is the evidence? Rheumatology (Oxford) 2009; 48(8):867-71.
2. Iaccarino L, Rampudda M, Canova M, et al. Mycophenolate mofetil: what is its place in the treatment of autoimmune rheumatic diseases? Autoimmun Rev 2007; 6(3):190-5.
3. Botsios C. Safety of tumor necrosis factor and interleukin-1 blocking agents in rheumatic diseases. Autoimmun Rev 2005; 4(3):162-70.
4. Bishop JF, Schimpff SC, Diggs CH, et al. Infections during intensive chemotherapy for non-Hodgkin's lymphoma. Ann Intern Med 1981; 95(5):549-55.
5. Anaissie EJ, Kontoyiannis DP, O'Brien S, et al. Infections in patients with chronic lymphocytic leukemia treated with fludarabine. Ann Intern Med 1998; 129(7):559-66.

Table 4. Important Identified Risk: Progressive multifocal leukoencephalopathy (All Indications)

Evidence for linking the risk to the medicine	Ruxience (rituximab) is a biosimilar medicinal product and the RP is MabThera. The evidence of the above-mentioned risk is derived from the MabThera RMP, which provides sufficient evidence from multiple sources (literature, clinical and/or post marketing).
Risk factors and risk groups	**RA** Progressive multifocal leukoencephalopathy (PML) has been reported in patients with autoimmune diseases (including systemic lupus erythematosus and RA) who have received immunosuppressive agents. **GPA/MPA** Cyclophosphamide is a risk factor for development of PML in GPA/MPA patients. **Pemphigus vulgaris** No information available. **NHL/CLL** PML almost exclusively occurs in immunocompromised patients. It may occur in patients with deficits in the humoral and/or cellular immune response such as lymphoproliferative diseases, myeloproliferative diseases, carcinomatous diseases and acquired immunodeficiency due to autoimmune diseases and immunosuppressive therapy. Fludarabine has been associated with an increased risk, possibly related to the induction a profound CD4+ lymphopenia.

Table 4. Important Identified Risk: Progressive multifocal leukoencephalopathy (All Indications)

Risk minimisation measures	Routine risk minimisation measures EU SmPC Section 4.4 *Special warnings and precautions for use* EU SmPC Section 4.8 *Undesirable effects* PL Section 4 *Possible side effects* *Medicine's legal status:* Medicinal product subject to restricted medical prescription. Additional risk minimisation measures (Non-oncology indications) PAC and educational material for patients and HCPs. The text of the PAC is included in the PI Annexes.

Table 5. Important Identified Risk: Hepatitis B reactivation (All Indications)

Evidence for linking the risk to the medicine	Ruxience (rituximab) is a biosimilar medicinal product and the RP is MabThera. The evidence of the above-mentioned risk is derived from the MabThera RMP, which provides sufficient evidence from multiple sources (literature, clinical and/or post marketing).
Risk factors and risk groups	Patients who have received immunosuppressive therapy for defined periods of time for haematological, oncological or rheumatological diseases and as long-term prophylaxis after bone marrow or solid organ transplantation are at an increased risk for HBV reactivation.[1] **NHL/CLL only** HBV reactivation is a well-documented complication of cytotoxic chemotherapy in patients with cancer. Pre-treatment liver function tests and HBV DNA levels have been shown not to correlate with the risk of subsequent development of HBV reactivation. However, male sex, younger age, HBeAg seropositivity, and diagnosis of lymphoma have been reported as risk factors for reactivation. Severe reactivation also appears more likely when the chemotherapy is significantly immunosuppressive, when the viral load is high, and in the presence of precore mutant variant of HBV.
Risk minimisation measures	Routine risk minimisation measures EU SmPC Section 4.4 *Special warnings and precautions for use* EU SmPC Section 4.8 *Undesirable effects* PL Section 2 *Warnings and precautions* PL Section 4 *Possible side effects* *Medicine's legal status:* Medicinal product subject to restricted medical prescription. Additional risk minimisation measures None.

1. Calabrese LH, Molloy ES, Huang D, et.al. Progressive Multifocal Leukoencephalopathy in Rheumatic Diseases. Arthritis & Rheumatism 2007; 56(7):2116-28.

Table 6. Important Identified Risk: Hypogammaglobulinaemia (Non-oncology indications)

Evidence for linking the risk to the medicine	Ruxience (rituximab) is a biosimilar medicinal product and the RP is MabThera. The evidence of the above-mentioned risk is derived from the PF-05280586, MabThera clinical trial data, and the MabThera RMP, which provides sufficient evidence from multiple sources (literature, clinical and/or post marketing).

Table 6. Important Identified Risk: Hypogammaglobulinaemia (Non-oncology indications)

Risk factors and risk groups	No clear baseline demographic or disease characteristics could be identified to potentially predict occurrence of hypogammaglobulinaemia.
Risk minimisation measures	Routine risk minimisation measures EU SmPC Section 4.4 *Special warnings and precautions for use* EU SmPC Section 4.8 *Undesirable effects* PL Section 4 *Possible side effects* *Medicine's legal status:* Medicinal product subject to restricted medical prescription. Additional risk minimisation measures None.

Table 7. Important Potential Risk: Malignant events (Non-oncology indications)

Evidence for linking the risk to the medicine	Ruxience (rituximab) is a biosimilar medicinal product and the RP is MabThera. The evidence of the above-mentioned risk is derived from the Ruxience and MabThera clinical trial data, and the MabThera RMP which provides sufficient evidence from multiple sources (literature, clinical and/or post marketing).
Risk factors and risk groups	**RA** An analysis of epidemiological data showed that RA patients remain at increased risk for overall malignancy, regardless of treatment, compared to the general population, having them a higher risk of lymphoma, lung cancer, and non-melanoma skin cancer (NMSC).[1,2,3] The risk of overall malignancy in treated RA patients is similar regardless of the treatment rituximab, tumour necrosis factor inhibitor (TNFi) and non-biologic disease modifying anti-rheumatic drugs (nbDMARDs). The literature search did not identify any publications on the risk of site-specific cancer among RA patients treated with rituximab. Received data from 3 RA patient registries [British Society of Rheumatology Biologics Register (BSRBR), Anti-Rheumatic Therapy in Sweden registry (ARTIS), and Rheumatoid Arthritis-Observation of Biologic Therapy (RABBIT)] suggested that RA patients treated with rituximab do not have a higher risk of overall malignancy, NMSC and possible other site-specific cancer compared to RA patients treated with nbDMARDs. **GPA/MPA** Epidemiologic data showed that patients with GPA or MPA are at higher risk of overall malignancy compared to the general population[4] Current immunosuppressive treatments with cyclophosphamide, corticosteroids, azathioprine, methotrexate or mycophenolate mofetil, have substantial long-term toxic effects (carcinogenic) and further on increases the risk of known malignancies associated with GPA/MPA. This increased risk of overall malignancy in GPA/MPA patients is mainly driven by the increased risk of NMSC, bladder cancer, leukaemia, and lymphoma.[5,6,7] There is substantial epidemiologic evidence of an elevated malignancy risk in GPA/MPA patients treated with cyclophosphamide, with some data suggest an increased risk even in the absence of immunosuppressive medication. **Pemphigus vulgaris** No information available.

Table 7. Important Potential Risk: Malignant events (Non-oncology indications)

Risk minimisation measures	Routine risk minimisation measures EU SmPC Section 4.4 *Special warnings and precautions for use* EU SmPC Section 4.8 *Undesirable effects* *Medicine's legal status:* Medicinal product subject to restricted medical prescription. Additional risk minimisation measures: None.

1. Smitten AL, Simon TA, Hochberg MC, et al. A meta-analysis of the incidence of malignancy in adult patients with rheumatoid arthritis. Arthritis Res Ther 2008; 10(2):R45.
2. Simon TA, Thompson A, Gandhi KK, et al. Incidence of malignancy in adult patients with rheumatoid arthritis: a meta-analysis. Arthritis Res Ther 2015; 17:212. (To read in conjuction with: Simon TA, Thompson A, Gandhi K, et al. Erratum to: Incidence of malignancy in adult patients with rheumatoid arthritis: a meta-analysis. Arthritis Res Ther 2016; 18: 100.)
3. Mercer LK, Green AC, Galloway JB et al. The influence of anti-TNF therapy upon incidence of keratinocyte skin cancer in patients with rheumatoid arthritis: longitudinal results from the British Society for Rheumatology Biologies Register. Ann Rheum Dis 2012; 71:869-74.
4. Faurschou M, Sorensen IJ, Mellemkjaer L, et al. Malignancies in Wegener's granulomatosis: incidence and relation to cyclophosphamide therapy in a cohort of 293 patients. J Rheumatol 2008; 35(1):100-5.
5. Pankhurst T, Savage CO, Gordon C, et al. Malignancy is increased in ANCA-associated vasculitis. Rheumatology 2004; 43 (12): 1532–5.
6. Knight A, Askling J, Ekbom A. Cancer incidence in a population-based cohort of patients with Wegener's granulomatosis. Int J Cancer 2002; 100(1):82-5.
7. Stone JH, Holbrook JT, Marriott MA, et al. Solid malignancies among patients in the Wegener's granulomatosis etanercept trial. Wegener's Granulomatosis Etanercept Trial Research Group. Arthritis Rheum 2006; 54(5):1608-18.

Table 8. Important Potential Risk: Impact on CV disease (Non-oncology indications)

Evidence for linking the risk to the medicine	Ruxience (rituximab) is a biosimilar medicinal product and the RP is MabThera. The evidence of the above-mentioned risk is derived from the Ruxience and MabThera clinical trial data, and the MabThera RMP which provides sufficient evidence from multiple sources (literature, clinical and/or post marketing).
Risk factors and risk groups	**RA** Patients with RA have a higher risk of CV disease (particularly ischaemic heart disease) than the general population. **GPA/MPA** An analysis by the European Vasculitis Study Group (EUVAS) of GPA/ MPA patients enrolled in four trials reported a standardized mortality ratio (SMR) of 2.6 (95% CI: 2.2, 3.1) when compared to age- and sex-matched general population controls and that cardiovascular disorders (CVD) was the most common cause of death after the first year (26% of all deaths).[1] **Pemphigus vulgaris** No information available.

Table 8. Important Potential Risk: Impact on CV disease (Non-oncology indications)

Risk minimisation measures	Routine risk minimisation measures EU SmPC Section 4.2 *Posology and method of administration* EU SmPC Section 4.4 *Special warnings and precautions for use* EU SmPC Section 4.8 *Undesirable effects* PL Section 2 *Warnings and precautions* PL Section 4 *Possible side effects* *Medicine's legal status:* Medicinal product subject to restricted medical prescription. Additional risk minimisation measures None.

1. Flossmann O, Berden A, de Groot K, et al. Long-term patient survival in ANCA-associated vasculitis. Ann Rheum Dis 2011; 70(3):488-94.

Table 9. Important Potential Risk: Relapses (GPA/MPA only)

Evidence for linking the risk to the medicine	Ruxience is a biosimilar medicinal product and the RP is MabThera. The evidence of the above-mentioned risk is derived from the MabThera RMP, which provides sufficient evidence from multiple sources (literature, clinical and/or post marketing).
Risk factors and risk groups	The time to relapse is shorter in patients who are proteinase 3 anti-neutrophil cytoplasm antibody (PR3-ANCA) positive, patients who have GPA, and patient who have relapsing disease at baseline.[1]
Risk minimisation measures	Routine risk minimisation measures EU SmPC Section 5.1, *Pharmacodynamic properties* *Medicine's legal status:* Medicinal product subject to restricted medical prescription. Additional risk minimisation measures None.

1. Stone JH, Merkel PA, Seo P, et al. Extended follow-up of treatment with rituximab versus cyclophosphamide for remission-induction of ANCA-associated vasculitis: which subsets are at greatest risk for flare? In: American College of Rheumatology; 4-9 Nov 2011; Chicago, IL. 2011: Abstr. 2432.

Table 10. Important Potential Risk: Off-label use in paediatric patients (All Indications)

Evidence for linking the risk to the medicine	Ruxience is a biosimilar medicinal product and the RP is MabThera. The evidence of the above-mentioned risk is derived from MabThera clinical trial data, and the MabThera RMP which provides sufficient evidence from multiple sources (literature, clinical and/or post marketing). - Study WA25615 in paediatric patients with severe GPA/MPA; - Intergroup B-NHL-2010 Study in advanced stage B-cell lymphoma (excluding primary mediastinal B-cell lymphoma), Burkitt or Burkitt-like Lymphoma/ leukaemia - US-based healthcare claims database (MarketScan); - Published literature - The RP's MAH safety database.

Table 10. Important Potential Risk: Off-label use in paediatric patients (All Indications)

Risk factors and risk groups	*Paediatric AI population*: Among children with rheumatic conditions, juvenile rheumatoid arthritis is the most frequently encountered rheumatic condition (53%), followed by spondyloarthropathy syndromes (13%), vasculitis (10%), systemic lupus erythematosus (SLE) (6%), isolated Raynaud's phenomenon (5%), dermatomyositis/polymyositis (5%), and scleroderma (2%).[1] The annual incidence rates of Juvenile Idiopathic Arthritis in Europe varied from 1.6 to 23 per 100,000 and the prevalence from 3.8 to 400 per 100,000.[2] The annual incidence of primary vasculitis in children and adolescents younger than 17 years is estimated around 22.8 (95% CI 20.9; 24.8) per 100,000.[3] Vasculitis in childhood is dominated by Henoch-Schönlein purpura (HSP) and Kawasaki disease (KD), accounting for 49% and 23% of all childhood vasculitis, respectively.[4] ANCA (anti-neutrophil cytoplasmic antibody) associated vasculitis (AAV) is relatively rare in children. Churg-Strauss Syndrome (also known as eGPA), is much less common in children than GPA and MPA.[5] Estimates of the incidence of GPA, MPA and Churg-Strauss Syndrome (CCS) are in the order of 20 new cases per million of the population per year and prevalence estimates range between 50 to 300 per million in countries in Western Europe, Australasia, Asia, and the Americas [6,7,8,9,10,11,12,13,14,15,16] with GPA being most prevalent.[16] Less than 15% of all GPA cases are reported in children. SLE in children represents 10-20% of all SLE cases.[17] Incidence rates for paediatric SLE have been reported to be 0.3-0.9 per 100,000 children-years, with prevalence estimates of 3.3-8.8 per 100,000 children.[18,4] Higher prevalence estimates have been reported in Native American and Asian populations.[18] The annual incidence for paediatric multiple sclerosis (MS) in Germany was estimated at 0.3 per 100,000 children,[18] at 0.51 per 100,000 person-years - in the US[19] and at 0.9 per 100,000 children - in Canada.[20] *Paediatric oncology population*: The number of paediatric patients with B-cell malignancies is extremely low. The age-adjusted incidence rate for lymphoma among European children is 1.51 per 100,000,[21] 9.4 per million (under 15 years of age) and 15.9 per million (adolescents aged 15-19 years) - for NHL;[22] in US (between the ages 0 to 14) - 1.58 per 100,000 for all lymphoma types and 0.61 per 100,000 for Non-Hodgkin lymphoma,[23] compare to adult rate of 22.4 per 100,000 - for all lymphoma types and 19.6 per 100,000 - for NHL. About 55% of these NHLs are mature B-cell lymphomas and thus potentially amenable to treatment with rituximab. Acute lymphoblastic Leukaemia (ALL) is the commonest lymphoid malignancy in childhood, especially between the ages of 1 and 4 years. There are approximately 5,000 cases of paediatric ALL every year in Europe, and 3,200 in the United States of America (USA).[24,25] The majority of these (80-85%) are of precursor B-cell origin but only about 11-50% - are likely to be CD20-positive and so potentially amenable to treatment with rituximab.[26,27,28] Follicular lymphoma and CLL are unlikely to have much effect on the incidence or pattern of off-label use in children since these are diseases of adults and do not occur in children.

Table 10. Important Potential Risk: Off-label use in paediatric patients (All Indications)

Risk factors and risk groups (*cont'd*)	*Paediatric Non-malignant haematological disorders*: The commonest non-malignant haematological disorder likely to be amenable to rituximab in children is idiopathic thrombocytopoenic purpura (ITP). The incidence in children is the same as in adults (30 per million per year).[29] Thrombotic thrombocytopoenic purpura (TTP) and acquired haemophilia appear to be extremely rare in children. However, congenital haemophilia with inhibitors does occur although it is not clear how it compares in incidence or severity with adults. The annual incidence of paediatric autoimmune haemolytic anaemia had been previously estimated to be around 0.2 per million individuals under 20 years of age, however the incidence in children and adolescents might be 10 to 20 times higher than previous estimates, given that in France there were a minimum of 15 new cases per year over the last 5 years, and around 15 million people with autoimmune haemolytic anaemia under 19 years old.[30] Results of rituximab treatment in children with non-malignant haematological disorders appear to be similar to that in adults with the same disorder and (as in adults) most data are from children with severe, chronic and/or refractory disease.
Risk minimisation measures	<u>Routine risk minimisation measures</u> EU SmPC Section 4.1 *Therapeutic indications* EU SmPC Section 4.2. *Posology and method of administration* *PL Section 2 Warnings and precautions* *Medicine's legal status:* Medicinal product subject to restricted medical prescription. <u>Additional risk minimisation measures</u> None.

1. Denardo BA, Tucker LB, Miller LC, et al. Demography of a regional pediatric rheumatology patient population. Affiliated Children's Arthritis Centers of New England. J Rheumatol 1994; 21(8):1553-61.
2. Thierry S, Fautrel B, Lemelle I, et al. Prevalence and incidence of juvenile idiopathic arthritis: a systematic review. Joint Bone Spine 2014; 81(2):112-7.
3. Gardner-Medwin JM, Dolezalova P, Cummins C, et al. Incidence of Henoch-Schönlein purpura, Kawasaki disease, and rare vasculitides in children of different ethnic origins. Lancet 2002; 360(9341):1197-202.
4. Malleson PN, Fung MY, Rosenberg AM, et al. The incidence of pediatric rheumatic diseases: results from the Canadian Pediatric Rheumatology Association Disease Registry. J Rheumatol 1996; 23(11):1981-7.
5. Weiss PF. Pediatric vasculitis. Pediatr Clin North Am 2012; 59(2):407-423.
6. Watts RA, Lane SE, Bentham G, et al. Epidemiology of Systemic Vasculitis. A Ten-Year Study in the United Kingdom. Arthritis & Rheumatism 2000;43(2): 414-9.
7. Gonzalez-Gay MA, Garcia-Porrua C, Guerrero J, et al. The epidemiology of the primary systemic vasculitides in northwest Spain: implications of the Chapel Hill Consensus Conference definitions. Arthritis Rheum 2003; 49(3):388-93.
8. Panagiotakis SH, Perysinakis GS, Kritikos H, et al. The epidemiology of primary systemic vasculitides involving small vessels in Crete (southern Greece): a comparison of older versus younger adult patients. Clin Exp Rheumatol 2009; 27(3):409-15.
9. Fujimoto S, Uezono S, Hisanaga S, et al. Incidence of ANCA-associated primary renal vasculitis in the Miyazaki Prefecture: the first population-based, retrospective, epidemiologic survey in Japan. Clin J Am Soc Nephrol 2006; 1(5):1016-22.
10. Sanchez AA, Acevedo EM, Sanchez CG, et al. Incidences of the primary systemic vasculitides in a Peruvian population: 233. J Clin Rheumatol 2006; 12(4):75.

Table 10. Important Potential Risk: Off-label use in paediatric patients (All Indications)

11. Ormerod AS, Cook MC. Epidemiology of primary systemic vasculitis in the Australian Capital Territory and south-eastern New South Wales. Intern Med J 2008; 38(11):816-23.
12. Mahr A, Guillevin L, Poissonnet M, et al. Prevalences of polyarteritis nodosa, microscopic polyangiitis, Wegener's granulomatosis, and Churg-Strauss syndrome in a French urban multiethnic population in 2000: a capture-recapture estimate. Arthritis Rheum 2004; 51(1):92-9.
13. Mohammad AJ, Jacobsson LT, Mahr AD, et al. Prevalence of Wegener's granulomatosis, microscopic polyangiitis, polyarteritis nodosa and Churg-Strauss syndrome within a defined population in southern Sweden. Rheumatology 2007; 46(8):1329-37.
14. Reinhold-Keller E, Zeidler A, Gutfleisch J, et al. Giant cell arteritis is more prevalent in urban than in rural populations: results of an epidemiological study of primary systemic vasculitides in Germany. Rheumatology 2000; 39(12):1396-402.
15. Watts RA, Carruthers DM, Scott DG. Epidemiology of systemic vasculitis: changing incidence or definition? Semin Arthritis Rheum 1995; 25(1):28-34.
16. Watts RA, Scott DG. Epidemiology of the vasculitides. Semin Respir Crit Care Med 2004; 25(5):455-64.
17. Kamphuis S, Silverman ED. Prevalence and burden of pediatric-onset systemic lupus erythematosus. Nat Rev Rheumatol 2010; 6(9):538-46.
18. Pohl D, Hennemuth I, von Kries R, et al. Paediatric multiple sclerosis and acute disseminated encephalomyelitis in Germany: results of a nationwide survey. Eur J Pediatr 2007; 166(5):405-12.
19. Langer-Gould A, Zhang JL, Chung J, et al. Incidence of acquired CNS demyelinating syndromes in a multiethnic cohort of children. Neurology 2011; 77(12):1143-8.
20. Banwell B, Kennedy J, Sadovnick D, et al. Incidence of acquired demyelination of the CNS in Canadian children. Neurology 2009; 72(3):232-9.
21. Furie R, Looney J, Rovin B, et al. Efficacy and safety of rituximab (RTX) in patients (PTS) with proliferative lupus nephritis (LN): results from the randomized, double-blind phase III LUNAR study. Ann Rheum Dis 2010; 69(Suppl 3):549.
22. Izarzugaza MI, Steliarova-Foucher E, Martos MC, et al. Non-Hodgkin's lymphoma incidence and survival in European children and adolescents (1978-1997): report from the Automated Childhood Cancer Information System project. Eur J Cancer 2006; 42(13):2050-63.
23. Furie R, Looney J, Rovin Bet al. Efficacy and Safety of Rituximab in Patients with Proliferative Lupus Nephritis: Results from the Randomized, Double-blind Phase III LUNAR (LUpus Nephritis Assessment with Rituximab) Study. Presentation ACR 2009
24. Jaffe ES, Harris NL, Stein H. World Health Organisation classification of tumors: pathology and genetics of tumors of haematopoietic and lymphoid tissues. Lyon: IARC Press; 2001.
25. Conter V, Rizzari C, Sala A, et al. Acute lymphoblastic leukemia. In: Paris, France: Orphanet Encyclopedia; 2004: 13 pages
26. Chu PG, Loera S, Huang Q, et al. Lineage determination of CD20- B-Cell neoplasms: an immunohistochemical study. Am J Clin Pathol 2006; 126(4):534-44.
27. Jeha S, Behm F, Pei D, et al. Prognostic significance of CD20 expression in childhood B-cell precursor acute lymphoblastic leukemia. Blood 2006; 108(10):3302-4.
28. Gudowius S, Recker K, Laws HJ, et al. Identification of candidate target antigens for antibody-based immunotherapy in childhood B-cell precursor ALL. Klin Paediatr 2006; 218(6):327-33.
29. Garvey B. Rituximab in the treatment of autoimmune haematological disorders. Br J Haematol 2008; 141(2):149-69.
30. Aladjidi N, Leverger G, Leblanc T, et al. New insights into childhood autoimmune hemolytic anemia: a French national observational study of 265 children. Haematologica 2011; 96(5):655-63.

Table 11. Important Potential Risk: Administration route error (NHL/CLL)

Evidence for linking the risk to the medicine	Ruxience is a biosimilar medicinal product and the reference product is MabThera. The evidence of the above-mentioned risk is derived from the MabThera RMP, which provides sufficient evidence from multiple sources (literature, clinical and/or post marketing). The RP SmPC provides recommendations to check the medicinal product labels to ensure that the appropriate formulation (IV or SC formulation) is being given to the patient, as prescribed. Based on the MabThera SC formulation clinical development, there were 2 patients randomized to the SC arm who were inadvertently administered rituximab IV via SC route. No AEs were associated with errors in these patients who remained in the study. Based on the reference product PM experience, the reporting rate of administration route error is very low.
Risk factors and risk groups	**NHL and CLL population** Administration route error could result from accidental substitution of the Branded rituximab (MabThera) which has subcutaneous (SC) formulation as well as intravenous formulations, being used instead of one of the rituximab biosimilars (including Ruxience), which are only available as IV formulations (eg, an error in the hospital pharmacy, or incorrect injection technique).
Risk minimisation measures	Routine risk minimisation measures EU SmPC Section 1: *Name of the Medicinal Product* EU SmPC Section 4.2: *Posology and method of administration* PL Section 3 The outer carton as well as the vial label of the product states: For intravenous use after dilution. *Medicine's legal status:* Medicinal product subject to restricted medical prescription. Additional risk minimisation measures The Physician information about Ruxience will contain information that the product should be administered intravenously (IV) only to avoid administration route error.

Table 12. Missing Information: Use in pregnancy and lactation (All Indications)

Risk minimisation measures	Routine risk minimisation measures EU SmPC Section 4.6*, Fertility, pregnancy and lactation* PL Section 2 *Warnings and precautions* *Medicine's legal status:* Medicinal product subject to restricted medical prescription. Additional risk minimisation measures None.

Table 13. Missing Information: Long-term use in GPA/MPA patients (GPA/MPA only)

Risk minimisation measures	Routine risk minimisation measures EU SmPC Section 5.1 *Pharmacodynamic properties* *Medicine's legal status:* Medicinal product subject to restricted medical prescription. Additional risk minimisation measures 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 authorization, specific obligations or required pharmacovigilance activities for Ruxience at the time of initial RMP submission.

II.C.2. Other Studies in Post-Authorisation Development Plan

None.