Summary of risk management plan for Ruxience

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 indications in adults are: rheumatoid arthritis (RA), granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), *Pemphigus vulgaris*, Non-Hodgkin's Lymphoma (NHL), and chronic lymphocytic leukaemia (CLL).

Additionally, Ruxience is indicated for the treatment of paediatric patients:

- aged ≥6 months to <18 years old, *in combination with chemotherapy, in previously untreated advanced stage CD20 positive diffuse large B-cell lymphoma, Burkitt lymphoma/Burkitt leukaemia (mature B-cell acute leukaemia) or Burkitt-like lymphoma.*

- aged ≥2 years to <18 years old, *in combination with glucocorticoids, for the induction of remission in severe, active GPA (Wegener's) and MPA.*

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

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 AEs will be 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 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	• Infections, including serious infections (All Indications) • Progressive multifocal leukoencephalopathy (All Indications) • Hepatitis B reactivation (All Indications) • Hypogammaglobulinaemia (Non-oncology Indications)
Important potential risks	• Relapses (GPA/MPA only) • Administration route error (NHL/CLL)
Missing information	• Long-term use in GPA/MPA patients (GPA/MPA only)

Abbreviations: 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: Infections, including serious infections (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 PF-05280586 and MabThera clinical trial data, and the MabThera risk management plan (RMP) which provides sufficient evidence from multiple sources (literature, clinical and/or post marketing).

Table 2. Important Identified Risk: Infections, including serious infections (All Indications)

Risk factors and risk groups	**RA and GPA/MPA** Patients with advanced rheumatoid arthritis (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 (MTX) appears to be associated with minimal, if any, increased infection risk.[2] 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.[3] Anti-tumour necrosis factor-α (TNF-α) agents like infliximab (IFX) are associated with an increased risk for tuberculosis (TB), hepatitis B virus (HBV) reactivation and opportunistic infections (OIs).[4] 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 by Bishop JF et al,[5]a higher infection rate in NHL patients was associated with granulocytopoenia 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 b_2-microglobulin level, low serum albumin level, low granulocyte count, and high serum creatinine concentration.[6] 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 (JC) virus/progressive multifocal leukoencephalopathy (PML), and this is probably related to the induction of profound CD4+ lymphopenia.

Table 2. Important Identified Risk: Infections, including serious infections (All Indications)

Risk factors and risk groups (*Cont'd*)	The risk of developing *Pneumocystis jiroveci* pneumonia (PJP) among human immunodeficiency virus (HIV) patients rises markedly when circulating cluster of differentiation 4 (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.
Risk minimisation measures	Routine risk minimisation measures European Union (EU) summary of product characteristics (SmPC) Section 4.4 *Special warnings and precautions for use* EU SmPC Section 4.8 *Undesirable effects* Package leaflet (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 healthcare professionals (HCPs). The text of the PAC is included in the package insert (PI) Annexes.

1. Dixon WG, Watson K, Lunt M, et al. Rates of serious infection, including site specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy. Arthritis Rheum 2006; 54(8):2368-76.
2. 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.
3. 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.
4. Botsios C. Safety of tumor necrosis factor and interleukin-1 blocking agents in rheumatic diseases. Autoimmun Rev 2005; 4(3):162-70.
5. 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.
6. 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 3. 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).

Table 3. Important Identified Risk: Progressive multifocal leukoencephalopathy (All Indications)

Risk factors and risk groups	**RA** PML has been reported in patients with autoimmune diseases (including SLE [systemic lupus erythematosus] and RA) who have received immunosuppressive agents. **GPA/MPA** Cyclophosphamide (CYC) is a risk factor for development of PML in GPA/MPA patients. **Pemphigus vulgaris** No information available. **NHL/CLL** PML almost exclusively occurs in immunocompromised patients. It may occur in patients with deficits in the humoral and/or cellular immune response such as lymphoproliferative diseases, myeloproliferative diseases, carcinomatous diseases and acquired immunodeficiency due to autoimmune diseases and immunosuppressive therapy. Fludarabine has been associated with an increased risk, possibly related to the induction a profound CD4+ lymphopenia.
Risk 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 4. 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).

Table 4. Important Identified Risk: Hepatitis B reactivation (All Indications)

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 of 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 deoxyribonucleic acid (DNA) levels have been shown not to correlate with the risk of subsequent development of HBV reactivation. However, male sex, younger age, hepatitis B e antigen (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 5. 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).
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 6. Important Potential Risk: Relapses (GPA/MPA only)

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

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). The RP SmPC provides recommendations to check the medicinal product labels to ensure that the appropriate formulation (intravenously [IV] or subcutaneous [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 RP 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 SC) which has subcutaneous 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).

Table 7. Important Potential Risk: Administration route error (NHL/CLL)

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 IV only to avoid administration route error.

Table 8. 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 authorisation, 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.