PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

RIXATHON 100 mg/10 ml (concentrate for solution for infusion)

RIXATHON 500 mg/50 ml (concentrate for solution for infusion)

WARNINGS

Infusion-related reactions: infusion-related deaths (death within 24 hours of the infusion) have been reported. These events appear as manifestations on an infusion-related complex which include hypoxia, lung infiltration, adult respiratory distress syndrome, myocardial infarction, ventricular fibrillation or cardiogenic shock. Nearly all fatal infusion-related events occurred were associated with the first infusion.

Tumour Lysis Syndrome (TLS): Acute renal failure requiring dialysis with instances of fatal outcome has been reported. Assessment of serum electrolytes and renal function is indicated in patients with rapid decrease in tumour volume.

Severe mucocutaneous reactions: Severe skin reactions such as Toxic Epidermal Necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome, some with fatal outcome, have been reported.

Progressive multifocal leukoencephalopathy (PML): Very rare cases of fatal PML have been reported. Patients must be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML.

Reactivation of hepatitis B: Cases of hepatitis B reactivation and reports of fulminant hepatitis, some of which were fatal have been reported.

Tuberculosis: Serious infections, including fatalities, can occur during therapy with rituximab. A diagnosis of any form of active tuberculosis should be explicitly excluded in patients considered for treatment with RIXATHON. (See Section 4.4).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10 mL concentrate for solution for infusion contains 100 mg rituximab (10 mg/mL).

Each 50 mL concentrate for solution for infusion contains 500 mg rituximab (10 mg/mL).

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Colourless to slightly yellowish solution with pH 6.3 – 6.7.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Non-Hodgkin's Lymphoma:

RIXATHON is indicated for the treatment of:

patients with relapsed or chemo-resistant low-grade or follicular, CD20-positive, B-cell non-Hodgkin's lymphoma

previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy

patients with follicular lymphoma as maintenance treatment, after response to induction therapy

patients with high grade CD20-positive diffuse large B-cell non-Hodgkin's lymphoma in combination with CHOP (Cyclophosphamide - C, Doxorubicin - H, Vincristine - O, Prednisone - P) chemotherapy.

Chronic Lymphocytic Leukaemia:

RIXATHON in combination with fludarabine and cyclophosphamide is indicated for the treatment of patients with previously untreated and relapsed/refractory chronic lymphocytic leukaemia (CLL).

Granulomatosis with polyangiitis and microscopic polyangiitis:

RIXATHON, in combination with glucocorticoids, is indicated for the treatment of patients with severely active Granulomatosis with polyangiitis (GPA, also known as Wegener's granulomatosis) and microscopic polyangiitis (MPA).

Pemphigus vulgaris

RIXATHON is indicated for the treatment of patients with moderate to severe pemphigus vulgaris (PV).

4.2. Posology and method of administration

Posology

The prepared RIXATHON solution should be administered as an IV infusion through a dedicated line.

The prepared infusion solution must not be administered as an IV injection or bolus infusion.

RIXATHON infusions should be administered in an environment where full resuscitation facilities are immediately available, and under the close supervision of an experienced healthcare professional.

RIXATHON is compatible with 0,9 % sodium chloride (normal saline) or 5 % dextrose (D5W) solutions for infusion.

Pre-medication consisting of an anti-pyretic and an antihistaminic, e.g. paracetamol and diphenhydramine, should always be administered 30 to 60 minutes prior to each infusion of RIXATHON.
Pre-medication with glucocorticoids should also be considered, particularly if RIXATHON is not given in combination with steroid-containing chemotherapy.
Patients should be closely monitored for the onset of cytokine release syndrome. In patients who develop evidence of severe reactions, especially severe dyspnoea, bronchospasm or hypoxia the infusion should immediately be interrupted. The patient should then be evaluated for evidence of tumour lysis syndrome including appropriate laboratory tests and, for pulmonary infiltration, with a chest X-ray. The infusion should not be restarted until complete resolution of all symptoms, and normalisation of laboratory values and chest X-ray findings. At this time, the infusion can be initially resumed at not more than one-half the previous rate. If the same severe adverse reactions occur for a second time, the decision to stop the treatment should be seriously considered on a case by case basis. See section 4.4.
Mild or moderate infusion-related reactions usually respond to a reduction in the rate of infusion. The infusion may be increased upon improvement of symptoms.

In patients with granulomatosis with polyangiitis (Wegener’s) or microscopic polyangiitis in disease remission or pemphigus vulgaris, premedication with 100 mg intravenous methylprednisolone should be completed 30 minutes prior to RIXATHON infusions to decrease the incidence and severity of infusion related reactions (IRRs).

In patients with granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis, methylprednisolone given intravenously for 1 to 3 days at a dose of 1000 mg per day is recommended prior to the first infusion of RIXATHON (the last dose of methylprednisolone may

be given on the same day as the first infusion of RIXATHON). This should be followed by oral prednisone 1 mg/kg/day (not to exceed 80 mg/day and tapered as rapidly as possible based on clinical need) during and after the 4-week induction course of RIXATHON treatment.
Pneumocystis jirovecii pneumonia (PCP) prophylaxis is recommended for patients with GPA/MPA or PV during and following RIXATHON treatment.

Low-grade/CD20 positive or follicular B-cell non-Hodgkin's lymphoma:

a) Initial treatment, weekly for 4 doses: The recommended dosage of RIXATHON used as a single agent/mono-therapy for adult patients is 375 mg/m^2 body surface area (BSA), administered as an intravenous infusion once weekly for four doses.

b) Initial treatment, bulky disease, weekly for 4 doses: The recommended dosage of RIXATHON used as a single agent/monotherapy for adult patients is 375 mg/m^2 body surface area (BSA), administered as an intravenous infusion once weekly for four doses.

c) Re-treatment following relapse, weekly for 4 doses: Patients who have responded to RIXATHON initially have been treated again with RIXATHON at a dose of 375 mg/m^2 body surface area, administered as an IV infusion once weekly for 4 weeks.

d) Combination therapy: The recommended dosage of RIXATHON in combination with chemotherapy for induction treatment of previously untreated or relapsed/refractory patients with follicular NHL is 375 mg/m^2 body surface area per cycle for 8 cycles (21 days/cycle).
RIXATHON should be administered on day 1 of each chemotherapy cycle, after IV administration of the glucocorticoid component of the chemotherapy, if applicable.

e) Maintenance therapy:

Previously untreated patients after response to induction treatment may receive maintenance therapy with RIXATHON given at 375 mg/m^2 body surface area once every 2 months until disease progression or for a maximum period of two years (12 infusions).

Relapsed/refractory patients after response to induction treatment may receive maintenance therapy with RIXATHON given at 375 mg/m^2 body surface area once every 3 months until disease progression or for a maximum period of two years.

High grade/CD20 positive or diffuse large B-cell non-Hodgkin's lymphoma:

RIXATHON should be used in combination with CHOP chemotherapy (R-CHOP). The recommended dosage is 375 mg/m^2 body surface area, administered on day 1 of each chemotherapy cycle for 8 cycles after *IV* administration of the glucocorticoid component of CHOP. The other components of CHOP should be given after the administration of RIXATHON.

First infusion: The recommended initial rate for infusion is 50 mg/hr; which can subsequently be escalated in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.

Subsequent infusions: Subsequent doses of RIXATHON can be infused at an initial rate of 100 mg/hr, and increased by 100 mg/hr increments at 30 minute intervals, to a maximum of 400 mg/hr.

Dosage adjustments during treatment:

No dose reductions of RIXATHON are recommended. When RIXATHON is given in combination with CHOP or CVP chemotherapy, standard dose reductions for the chemotherapeutic agents should be applied.

Chronic Lymphocytic Leukaemia (CLL):

Pre-medication consisting of an analgesic/anti-pyretic (e.g. paracetamol) and an antihistaminic (e.g. diphenhydramine) should always be administered before each infusion of RIXATHON. Pre-medication with glucocorticoids should also be considered, particularly if RIXATHON is not given in combination with steroid-containing chemotherapy.

Prophylaxis with adequate hydration and administration of uricostatics starting 48 hours prior to start of therapy is recommended for CLL patients to reduce the risk of tumour lysis syndrome. For CLL patients whose lymphocyte counts are > 25 x 10^9 /L it is recommended to administer prednisone/prednisolone 100 mg IV shortly before infusion with RIXATHON to decrease the rate and severity of acute infusion reactions and/or cytokine release syndrome.

The recommended dosage of RIXATHON in combination with chemotherapy for previously untreated and relapsed/refractory patients is 375 mg/m^2 body surface area administered on day 0 of the first treatment cycle (the day before chemotherapy) followed by 500 mg/m^2 body surface area administered on day 1 of each subsequent cycle for 6 cycles in total. The chemotherapy should be given after RIXATHON infusion.

Granulomatosis with polyangiitis and microscopic polyangiitis

The recommended dosage of RIXATHON for treatment of GPA and MPA is 375 mg/m^2 body surface area, administered as an IV infusion once weekly for 4 weeks.

Methylprednisolone 1 000 mg IV per day for 1 to 3 days is recommended in combination with RIXATHON to treat severe vasculitis symptoms, followed by oral prednisone 1 mg/kg/day (not to exceed 80 mg/day, and tapered as rapidly as possible per clinical need) during and after RIXATHON treatment.

First infusion: The recommended initial infusion rate for RIXATHON is 50 mg/hr; subsequently, the rate can be escalated in 50 mg/hr increments every 30 minutes to a maximum of 400 mg/hr.

Subsequent infusions: Subsequent infusions of RIXATHON can be started at a rate of 100 mg/hr and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr. *Pneumocystis jiroveci pneumonia* (PCP) prophylaxis is recommended for patients with GPA and MPA during and following RIXATHON treatment, as appropriate.

Pemphigus vulgaris

The recommended dosage of RIXATHON for the treatment of pemphigus vulgaris is 1000 mg administered as an IV infusion followed two weeks later by a second 1000 mg IV infusion in combination with a tapering course of glucocorticoids.

Maintenance treatment

A maintenance infusion of 500 mg IV should be administered at months 12 and 18, and then every 6 months thereafter if needed, based on clinical evaluation.

Treatment of relapse

In the event of relapse, patients may receive 1000 mg IV. The healthcare provider should also consider resuming or increasing the patient's glucocorticoid dose based on clinical evaluation. Subsequent infusions may be administered no sooner than 16 weeks following the previous infusion.

Special Dosage Instructions:

Children and adolescents: The safety and efficacy of RIXATHON in children and adolescents have not been established.

Elderly: No dose adjustment is required in elderly patients (aged > 65 years).

Method of Administration

First infusion

The recommended initial rate for infusion is 50 mg/hr; after the first 30 minutes, it can be escalated in 50 mg/h increments every 30 minutes, to a maximum of 400 mg/hr.

Subsequent infusions

Subsequent doses of RIXATHON can be infused at an initial rate of 100 mg/hr, and increased by 100 mg/hr increments at 30 minutes intervals, to a maximum of 400 mg/hr.

Withdraw the required amount of RIXATHON under aseptic conditions and dilute to a calculated rituximab concentration of 1 - 4 mg/mL in an infusion bag containing sterile, non-pyrogenic 0,9 % normal saline solution or 5 % dextrose solution (D5W) for infusion. To mix the solution, gently invert the bag to avoid foaming. Parenteral medications should be inspected visually for particulate matter or discolouration prior to administration.

4.3. Contraindications

Hypersensitivity to the active substance or to murine proteins, or to any of the other excipients listed in section 6.1.

Active, severe infections (see section 4.4).

Patients in a severely immunocompromised state.

Severe heart failure (New York Heart Association Class IV) or severe, uncontrolled cardiac disease (see section 4.4 regarding other cardiovascular diseases).

4.4. Special warnings and precautions for use

Traceability:

In order to improve traceability of biological medicinal products, the tradename and batch number of the administered product should be clearly recorded.

Progressive multifocal leukoencephalopathy:

All patients treated with rituximab for GPA, MPA or pemphigus vulgaris must be given the patient alert card with each infusion. The alert card contains important safety information for patients regarding potential increased risk of infections, including progressive multifocal leukoencephalopathy (PML).

Very rare cases of fatal PML have been reported following use of rituximab. Patients must be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML. If PML is suspected, further dosing must be suspended until PML has been excluded. The clinician should evaluate the patient to determine if the symptoms are indicative of neurological dysfunction, and if so, whether these symptoms are possibly suggestive of PML. Consultation with a Neurologist should be considered as clinically indicated.

If any doubt exists, further evaluation, including MRI scan preferably with contrast, cerebrospinal fluid (CSF) testing for JC Viral DNA and repeat neurological assessments, should be considered.

The medical practitioner should be particularly alert to symptoms suggestive of PML that the patient may not notice (e.g. cognitive, neurological or psychiatric symptoms). Patients should also be advised to inform their partner or caregivers about their treatment, since they may notice symptoms that the patient is not aware of.

If a patient develops PML, the dosing of rituximab must be permanently discontinued.

Following reconstitution of the immune system in immunocompromised patients with PML, stabilisation or improved outcome has been seen. It remains unknown if early detection of PML and suspension of rituximab therapy may lead to similar stabilisation or improved outcome.

Non-Hodgkin's lymphoma and chronic lymphocytic leukaemia:

Infusion-related reactions:

Rituximab is associated with infusion-related reactions, which may be related to release of cytokines and/or other chemical mediators. Cytokine release syndrome may be clinically indistinguishable from acute hypersensitivity reactions.

This set of reactions which includes syndrome of cytokine release, tumour lysis syndrome and anaphylactic and hypersensitivity reactions are described below. They are not specifically related to the route of administration of rituximab and can be observed with both formulations.

Severe infusion-related reactions with fatal outcome have been reported during post-marketing use of the rituximab intravenous formulation, with an onset ranging within 30 minutes to 2 hours after starting the first rituximab intravenous infusion. They were characterised by pulmonary events and in some cases included rapid tumour lysis and features of tumour lysis syndrome in addition to fever, chills, rigors, hypotension, urticaria, angioedema and other symptoms (see section 4.8).

Severe cytokine release syndrome is characterised by severe dyspnoea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. This syndrome may be associated with some features of tumour lysis syndrome such as hyperuricaemia, hyperkalaemia, hypocalcaemia, hyperphosphataemia, acute renal failure, elevated lactate dehydrogenase (LDH) and may be associated with acute respiratory failure and death. The acute respiratory failure may be accompanied by events such as pulmonary interstitial infiltration or oedema, visible on a chest X-ray. The syndrome frequently manifests itself within one or two hours of initiating the first infusion. 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. Patients who develop severe cytokine release syndrome should have their infusion interrupted immediately (see section 4.2) and should receive aggressive symptomatic treatment. Since initial improvement of clinical symptoms may be followed by deterioration, these patients should be closely monitored until tumour lysis syndrome and pulmonary infiltration have been resolved or ruled out. Further treatment of patients after complete resolution of signs and symptoms has rarely resulted in repeated severe cytokine release syndrome.

Patients with a high tumour burden or with a high number (≥ 25 x 109/L) of circulating malignant cells such as patients with CLL, who may be at higher risk of especially severe cytokine release syndrome, should be treated with extreme caution. 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 or a split dosing over two days during the first cycle and any subsequent cycles if the lymphocyte count is still >25 x 10^9/L.

Infusion-related adverse reactions of all kinds have been observed in 77 % of patients treated with RIXATHON (including cytokine release syndrome accompanied by hypotension and bronchospasm in 10 % of patients) see section 4.8. These symptoms are usually reversible with interruption of RIXATHON infusion and administration of an anti-pyretic, an antihistaminic and occasionally oxygen, intravenous saline or bronchodilators, and glucocorticoids if required. Please see cytokine release syndrome above for severe reactions.

Anaphylactic and other hypersensitivity reactions have been reported following the intravenous administration of proteins to patients. In contrast to cytokine release syndrome, true hypersensitivity reactions typically occur within minutes after starting infusion. Medicinal products for the treatment of hypersensitivity reactions, e.g. epinephrine (adrenaline), antihistamines and glucocorticoids, should be available for immediate use in the event of an allergic reaction during administration of

RIXATHON. Clinical manifestations of anaphylaxis may appear similar to clinical manifestations of the cytokine release syndrome (described above). Reactions attributed to hypersensitivity have been reported less frequently than those attributed to cytokine release.

Additional reactions reported in some cases were myocardial infarction, atrial fibrillation, pulmonary oedema and acute reversible thrombocytopenia.

Since hypotension may occur during rituximab administration, consideration should be given to withholding antihypertensive medicines 12 hours prior to the rituximab infusion.

Cardiac disorders:

Angina pectoris, cardiac arrhythmias such as atrial flutter and fibrillation, heart failure and/or myocardial infarction have occurred in patients treated with RIXATHON. Therefore, patients with a history of cardiac disease and/or cardiotoxic chemotherapy should be monitored closely.

Haematological toxicities:

Although RIXATHON is not myelosuppressive in monotherapy, caution should be exercised when considering treatment of patients with neutrophils < 1.5 x 109/L and/or platelet counts < 75 x 109/L as clinical experience in this population is limited. Rituximab has been used in 21 patients who underwent autologous bone marrow transplantation and other risk groups with a presumable reduced bone marrow function without inducing myelotoxicity.

Regular full blood counts, including neutrophil and platelet counts, should be performed during RIXATHON therapy.

Infections:

Serious infections, including fatalities, can occur during therapy with RIXATHON (see section 4.8). RIXATHON should not be administered to patients with an active, severe infection (e.g. tuberculosis, sepsis and opportunistic infections, see section 4.3).

Medical practitioners should exercise caution when considering the use of RIXATHON in patients with a history of recurring or chronic infections or with underlying conditions, which may further predispose patients to serious infection (see section 4.8).

Cases of hepatitis B reactivation have been reported in subjects receiving rituximab including fulminant hepatitis with fatal outcome. The majority of these subjects were also exposed to cytotoxic chemotherapy. Limited information from one study in relapsed/refractory CLL patients suggests that rituximab treatment may also worsen the outcome of primary hepatitis B infections. Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with rituximab. At minimum this should include HBsAg-status and HBcAb-status. These can be complemented with other appropriate markers as per local guidelines. Patients with active hepatitis B disease should not be treated with rituximab. Patients with positive hepatitis B serology (either HBsAg or HBcAb) should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation.

Very rare cases of progressive multifocal leukoencephalopathy (PML) have been reported during post-marketing use of rituximab in NHL and CLL (see section 4.8). The majority of patients had received rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant.

Immunisations:

The safety of immunisation with live viral vaccines, following rituximab therapy has not been studied for NHL and CLL patients and vaccination with live virus vaccines is not recommended. Patients treated with rituximab may receive non-live vaccinations; however, with non-live vaccines response

rates may be reduced. In a non-randomised study, adult patients with relapsed low-grade NHL who received RIXATHON monotherapy when compared to healthy untreated controls had a lower rate of response to vaccination with tetanus recall antigen (16 % vs. 81 %) and Keyhole Limpet Haemocyanin (KLH) neoantigen (4 % vs. 76 % when assessed for > 2-fold increase in antibody titer). For CLL patients, similar results are assumable considering similarities between both diseases but that has not been investigated in clinical trials.

Mean pre-therapeutic antibody titres against a panel of antigens (*Streptococcus pneumoniae*, *influenza A,* mumps, rubella, varicella) were maintained for at least 6 months after treatment with rituximab.

Skin reactions:

Severe skin reactions such as Toxic Epidermal Necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome, some with fatal outcome, have been reported (see section 4.8). In case of such an event, with a suspected relationship to rituximab, treatment should be permanently discontinued.

Paediatric population:

Only limited data are available for patients under 3 years of age. See section 5.1 for further information.

Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), and pemphigus vulgaris:

Infusion-related reactions:

RIXATHON is associated with infusion related reactions (IRRs), which may be related to release of cytokines and/or other chemical mediators.

Most infusion-related events reported were mild to moderate in severity. The most common symptoms were allergic reactions like headache, pruritus, throat irritation, flushing, rash, urticaria, hypertension, and pyrexia. In general, the proportion of patients experiencing any infusion reaction was higher following the first infusion than following the second infusion of any treatment course. The incidence of IRR decreased with subsequent courses (see section 4.8). The reactions reported were usually reversible with a reduction in rate, or interruption, of rituximab infusion and administration of an anti-pyretic, an antihistamine, and, occasionally, oxygen, intravenous saline or bronchodilators, and glucocorticoids if required. Closely monitor patients with pre-existing cardiac conditions and those who experienced prior cardiopulmonary adverse reactions.
Depending on the severity of the IRR and the required interventions, temporarily or permanently discontinue RIXATHON. In most cases, the infusion can be resumed at a 50 % reduction in rate (e.g. from 100 mg/h to 50 mg/h) when symptoms have completely resolved.
Medicines for the treatment of hypersensitivity reactions, e.g. epinephrine (adrenaline), antihistamines and glucocorticoids, should be available for immediate use in the event of an allergic reaction during administration of RIXATHON.
There are no data on the safety of rituximab in patients with moderate heart failure (NYHA class III) or severe, uncontrolled cardiovascular disease. In patients treated with rituximab, the occurrence of pre-existing ischemic cardiac conditions becoming symptomatic, such as angina pectoris, has been observed, as well as atrial fibrillation and flutter.
Therefore, in patients with a known cardiac history, and those who experienced prior cardiopulmonary adverse reactions, the risk of cardiovascular complications resulting from infusion reactions should be considered before treatment with RIXATHON and patients closely monitored during administration. Since hypotension may occur during RIXATHON infusion, consideration should be given to withholding anti-hypertensive medications 12 hours prior to the RIXATHON infusion.

Cardiac disorders:

Angina pectoris, cardiac arrhythmias such as atrial flutter and fibrillation, heart failure and/or myocardial infarction have occurred in patients treated with RIXATHON. Therefore, patients with a history of cardiac disease should be monitored closely (see Infusion-related reactions, above).

Infections:

Based on the mechanism of action of RIXATHON and the knowledge that B cells play an important role in maintaining normal immune response, patients have an increased risk of infection following RIXATHON therapy (see section 5.1).

Serious infections, including fatalities, can occur during therapy with RIXATHON (see section 4.8). RIXATHON should not be administered to patients with an active, severe infection (e.g. tuberculosis, sepsis and opportunistic infections, see section 4.3) or severely immunocompromised patients (e.g. where levels of CD4 or CD8 are very low). Medical practitioners should exercise 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, e.g. hypogammaglobulinaemia (see section 4.8). It is recommended that immunoglobulin levels are determined prior to initiating treatment with RIXATHON.

Patients reporting signs and symptoms of infection following RIXATHON therapy should be promptly evaluated and treated appropriately. Before giving a subsequent course of RIXATHON treatment, patients should be re-evaluated for any potential risk for infections.

Very rare cases of fatal progressive multifocal leukoencephalopathy (PML) have been reported following use of RIXATHON for the treatment of autoimmune diseases including Systemic Lupus Erythematosus (SLE) and vasculitis.

Hepatitis B Infections:

Cases of hepatitis B reactivation, including those with a fatal outcome, have been reported in GPA and MPA patients receiving RIXATHON.

Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with rituximab. At minimum, this should include HBsAg-status and HBcAb-status. These can be complemented with other appropriate markers as per local guidelines. Patients with active hepatitis B disease should not be treated with RIXATHON. Patients with positive hepatitis B serology (either HBsAg or HBcAb) should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation.

Late neutropenia:

Measure blood neutrophils prior to each course of RIXATHON, and regularly up to 6-months after cessation of treatment, and upon signs or symptoms of infection (see section 4.8).

Skin reactions:

Severe skin reactions such as Toxic Epidermal Necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome, some with fatal outcome, have been reported (see section 4.8). In case of such an event with a suspected relationship to RIXATHON, treatment should be permanently discontinued.

Immunisation:

Medical practitioners should review the patient's vaccination status and patients should, if possible, be brought up-to-date with all immunisations in agreement with current immunisation

guidelines prior to initiating rituximab therapy. Vaccination should be completed at least 4 weeks prior to first administration of RIXATHON.

The safety of immunisation with live viral vaccines following rituximab therapy has not been studied. Therefore, vaccination with live virus vaccines is not recommended whilst on RIXATHON or whilst peripherally B cell depleted.

Patients treated with rituximab may receive non-live vaccinations; however, response rates to non-live vaccines may be reduced.

Should non-live vaccinations be required whilst receiving RIXATHON therapy, these should be completed at least 4 weeks prior to commencing the next course of RIXATHON.

Malignancy:

Immunomodulatory medicines may increase the risk of malignancy.

HIV and tuberculosis testing and risks of RIXATHON

A diagnosis of any form of active tuberculosis should be explicitly excluded in patients considered for treatment with RIXATHON. Furthermore, a history of previous tuberculosis, HIV-infection, or a diagnosis of latent TB infection pose a risk for reactivation of tuberculosis disease and appropriate preventive therapy is indicated, regardless of HIV-status. Diagnosis and treatment of latent infection, following national guidelines, should be initiated prior to use of RIXATHON.

People initiating RIXATHON treatment, who initially tested negative for active or latent tuberculosis, should be systematically tested for latent TB infection during treatment with RIXATHON, and preventive treatment instituted if indicated.

Excipients:

RIXATHON 100 and 500 contains 90 mg and 450 mg sodium per 10 ml and 50 ml vial respectively. This needs to be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Currently, there are limited data on possible drug interactions with rituximab.

In CLL patients, co-administration with rituximab did not appear to have an effect on the pharmacokinetics of fludarabine or cyclophosphamide. In addition, there was no apparent effect of fludarabine and cyclophosphamide on the pharmacokinetics of rituximab.

Patients with human anti-mouse antibody (HAMA) or anti-drug antibody (ADA) titres may have allergic or hypersensitivity reactions when treated with other diagnostic or therapeutic monoclonal antibodies.

4.6 Fertility, pregnancy and lactation

Contraception in males and females:

Due to the long retention time of rituximab in B cell depleted patients, women of childbearing potential should use effective contraceptive methods during and for 12 months following treatment with RIXATHON.

Pregnancy:

IgG immunoglobulins are known to cross the placental barrier.

B cell levels in human neonates following maternal exposure to RIXATHON have not been studied in clinical trials. There are no adequate and well-controlled data from studies in pregnant women, however transient B-cell depletion and lymphocytopenia have been reported in some infants born to mothers exposed to RIXATHON during pregnancy. Similar effects have been observed in

animal studies (see section 5.3). For these reasons, RIXATHON should not be administered to pregnant women unless the possible benefit outweighs the potential risk.

Breast-feeding:

Whether rituximab is excreted in human milk is not known. However, because maternal IgG is excreted in human milk, and rituximab was detectable in milk from lactating monkeys, women should not breastfeed while treated with RIXATHON and for 12 months following RIXATHON treatment.

Fertility:

Animal studies did not reveal deleterious effects of rituximab on reproductive organs.

4.7 Effects on ability to drive and use machines

No studies on the effects of RIXATHON on the ability to drive and use machines have been performed, although the pharmacological activity and adverse reactions reported to date suggest that RIXATHON would have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Experience from non-Hodgkin's lymphoma and chronic lymphocytic leukaemia in adults:

Summary of the safety profile:

The overall safety profile of rituximab in non-Hodgkin's lymphoma and CLL is based on data from patients from clinical trials and from post-marketing surveillance. These patients were treated either with rituximab monotherapy (as induction treatment or maintenance treatment following induction treatment) or in combination with chemotherapy.

The most frequently observed adverse reactions (ADRs) in patients receiving rituximab were IRRs, which occurred in the majority of patients during the first infusion. The incidence of infusion-related symptoms decreases substantially with subsequent infusions and is less than 1 % after eight doses of rituximab.

Infectious events (predominantly bacterial and viral) occurred in approximately 30-55 % of patients during clinical trials in patients with NHL and in 30-50 % of patients during clinical trials in patients with CLL.

The most frequently reported or observed **serious** adverse reactions were:

IRRs (including cytokine-release syndrome, tumour-lysis syndrome), see section 4.4.

Infections, see section 4.4.

Cardiovascular events, see section 4.4.

Other serious ADRs reported include hepatitis B reactivation and PML (see section 4.4.).

Table 1: ADRs reported in clinical trials or during post marketing surveillance in patients with NHL and CLL disease treated with rituximab monotherapy/maintenance or in combination with chemotherapy:

System Organ Class	Frequent	Less frequent	Frequency not known
Infections and infestations	Bacterial infections, viral infections, +bronchitis, sepsis, +pneumonia, +febrile infection, +herpes zoster, +respiratory tract infection, fungal infections, infections of Unknown aetiology, +acute bronchitis, +sinusitis, hepatitis B[1]	serious viral infection[2], PML, Pneumocystis, jirovecii	--
Blood and lymphatic system disorders	neutropenia, leucopenia, +febrile neutropenia, +thrombocytopenia anaemia, +pancytopenia, +granulocytopenia	coagulation disorders, aplastic anaemia, haemolytic anaemia, lymphadenopathy transient increase in	late neutropenia[3]
Immune system disorders	infusion-related reactions[4], angioedema hypersensitivity	Anaphylaxis tumour lysis syndrome, cytokine release syndrome[4], serum sickness	infusion-related acute reversible Thrombocytopenia [4]
Metabolism and nutrition disorders	hyperglycaemia, weight decrease, peripheral oedema, face oedema, increased LDH, hypocalcaemia	--	--
Psychiatric disorders	--	depression, nervousness	--
Nervous system	paraesthesia, hypoaesthesia,	Dysgeusia, peripheral	cranial

disorders	agitation, insomnia, vasodilatation, dizziness, anxiety	neuropathy, facial nerve palsy[5]	Neuropathy, loss of other senses[5]
Eye disorders	lacrimation disorder, conjunctivitis	severe vision loss[5]	--
Ear and labyrinth disorders	tinnitus, ear pain	--	hearing loss[5]
Cardiac disorders	+myocardial infarction[4 and 6], arrhythmia, +atrial fibrillation, tachycardia, +cardiac disorder	+left ventricular failure, +supraventricular tachycardia, severe cardiac disorders, [4 and 6] heart failure,[4 and 6] +ventricular tachycardia, +angina, +myocardial ischaemia, bradycardia	--
Vascular disorders	hypertension, orthostatic hypotension, hypotension	vasculitis (predominately cutaneous), leukocytoclastic vasculitis	--

Respiratory, thoracic and mediastinal disorders	Bronchospasm[4], respiratory disease, chest pain, dyspnoea, increased cough, rhinitis	asthma, bronchiolitis obliterans, lung disorder, hypoxia, interstitial lung disease,[7] respiratory failure[4]	lung infiltration
Gastrointestinal disorders	Nausea, vomiting, diarrhoea, abdominal pain, dysphagia, stomatitis, constipation, dyspepsia, anorexia, throat irritation	abdominal enlargement, gastro-intestinal perforation[7]	--
Skin and Subcutaneous tissue disorders	pruritus, rash, +alopecia, urticaria, sweating, night sweats, +skin disorder	severe bullous skin reactions, Stevens- Johnson syndrome, toxic Epidermal necrolysis (Lyell's syndrome)[7]	--
Musculo skeletal, connective tissue disorders	hypertonia, myalgia, arthralgia, back pain, neck pain, pain	--	--
Renal and urinary disorders	--	--	renal failure[4]
General disorders and	fever, chills, asthenia, headache, tumour pain, flushing, malaise,	infusion site pain	--

administration site conditions	cold syndrome, +fatigue, +shivering, +multi- organ failure[4]		
Investigations	decreased IgG levels	--	--

For each term, the frequency count was based on reactions of all grades (from mild to severe), except for terms marked with "+" where the frequency count was based only on severe (≥ grade 3 NCI common toxicity criteria) reactions. Only the highest frequency observed in the trials is reported

[1] includes reactivation and primary infections; frequency based on R-FC regimen in relapsed/refractory CLL

[2] see also section infection below

[3] see also section haematologic adverse reactions below

[4] see also section infusion-related reactions below. Rarely fatal cases reported

[5] signs and symptoms of cranial neuropathy. Occurred at various times up to several months after completion of rituximab therapy

[6] observed mainly in patients with prior cardiac condition and/or cardiotoxic chemotherapy and were mostly associated with infusion-related reactions

[7] includes fatal cases

The following terms have been reported as adverse events during clinical trials, however, were reported at a similar or lower incidence in the rituximab arms compared to control arms: hematotoxicity, neutropenic infection, urinary tract infection, sensory disturbance, pyrexia.

Signs and symptoms suggestive of an infusion-related reaction were reported in more than 50 % of patients in clinical trials, and were predominantly seen during the first infusion, usually in the

first one to two hours. These symptoms mainly comprised fever, chills and rigors. Other symptoms included flushing, angioedema, bronchospasm, vomiting, nausea, urticaria/rash, fatigue, headache, throat irritation, rhinitis, pruritus, pain, tachycardia, hypertension, hypotension, dyspnoea, dyspepsia, asthenia and features of tumour lysis syndrome. Severe infusion-related reactions (such as bronchospasm, hypotension) occurred in up to 12 % of the cases.

Additional reactions reported in some cases were myocardial infarction, atrial fibrillation and pulmonary oedema and acute reversible thrombocytopenia. Exacerbations of pre-existing cardiac conditions such as angina pectoris or congestive heart failure or severe cardiac events (heart failure, myocardial infarction, atrial fibrillation), pulmonary oedema, multi-organ failure, tumour lysis syndrome, cytokine release syndrome, renal failure, acute respiratory distress syndrome, ventricular fibrillation, cardiogenic shock and respiratory failure were reported at lower or unknown frequencies.

The incidence of infusion-related symptoms decreased substantially with subsequent infusions and is <1 % of patients by the eighth cycle of rituximab (containing) treatment.

Description of selected adverse reactions:

Infections

Rituximab induces B-cell depletion in about 70 to 80 % of patients, but was associated with decreased serum immunoglobulins only in a minority of patients.

Localised candida infections as well as Herpes zoster was reported at a higher incidence in the rituximab-containing arm of randomized studies. Severe infections were reported in about 4 % of patients treated with rituximab monotherapy. Higher frequencies of infections overall, including grade 3 or 4 infections, were observed during rituximab maintenance treatment up to 2 years

when compared to observation. There was no cumulative toxicity in terms of infections reported over a 2-year treatment period. In addition, other serious viral infections either new, reactivated or exacerbated, some of which were fatal, have been reported with rituximab treatment. The majority of patients had received rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant. Examples of these serious viral infections are infections caused by the herpes viruses (Cytomegalovirus, Varicella Zoster Virus and Herpes Simplex Virus), JC virus (progressive multifocal leukoencephalopathy (PML)) and hepatitis C virus. Cases of fatal PML that occurred after disease progression and retreatment have also been reported in clinical trials. Cases of hepatitis B reactivation have been reported, the majority of which were in subjects receiving rituximab in combination with cytotoxic chemotherapy. In patients with relapsed/refractory CLL, the incidence of grade 3/4 hepatitis B infection (reactivation and primary infection) was 2 % in R-FC vs. 0 % FC.

Progression of Kaposi's sarcoma has been observed in rituximab exposed patients with pre-existing Kaposi's sarcoma. These cases occurred in non-approved indications and the majority of patients were HIV positive.

Haematologic Adverse Reactions

In clinical trials with rituximab monotherapy given for 4 weeks, haematological abnormalities occurred in a minority of patients and were usually mild and reversible. Severe (grade 3/4) neutropenia was reported in 4,2 %, anaemia in 1,1 % and thrombocytopenia in 1,7 % of the patients. During rituximab maintenance treatment for up to 2 years, leucopenia (5 % vs. 2 %, grade 3/4) and neutropenia (10 % vs. 4 %, grade 3/4) were reported at a higher incidence when compared to observation. The incidence of thrombocytopenia was low (<1, grade 3/4 %) and was not different between treatment arms. In studies with rituximab in combination with chemotherapy, grade 3/4 leucopenia (R-CHOP 88 % vs. CHOP 79 %, R-FC 23 % vs. FC 12 %), neutropenia (R

CVP 24 % vs. CVP 14 %; R-CHOP 97 % vs. CHOP 88 %, R-FC 30 % vs. FC 19 % in previously untreated CLL), pancytopenia (R-FC 3 % vs. FC 1 % in previously untreated CLL) were usually reported with higher

frequencies when compared to chemotherapy alone. However, the higher incidence of neutropenia in patients treated with rituximab and chemotherapy was not associated with a higher incidence of infections and infestations compared to patients treated with chemotherapy alone. Studies in previously untreated and relapsed/refractory CLL have established that in up to 25 % of patients treated with R-FC neutropenia was prolonged (defined as neutrophil count remaining below 1 x 10^9 /L between day 24 and 42 after the last dose) or occurred with a late onset (defined as neutrophil count 1x10^9 /L later than 42 days after last dose in patients with no previous prolonged neutropenia or who recovered prior to day 42) following treatment with rituximab plus FC. There were no differences reported for the incidence of anaemia. Some cases of late neutropenia occurring more than four weeks after the last infusion of rituximab were reported. In the CLL first-line study, Binet stage C patients experienced more adverse events in the R-FC arm compared to the FC arm (R-FC 83 % vs. FC 71 %). In the relapsed/refractory CLL study, grade 3/4 thrombocytopenias was reported in 11 % of patients in the R-FC group compared to 9 % of patients in the FC group.

Cardiovascular adverse reactions

Cardiovascular reactions during clinical trials with rituximab monotherapy were reported in 18,8 % of patients with the most frequently reported events being hypotension and hypertension. Cases of grade 3 or 4 arrhythmia (including ventricular and supraventricular tachycardia) and angina pectoris during infusion were reported. During maintenance treatment, the incidence of grade 3/4 cardiac disorders was comparable between patients treated with rituximab and observation. Cardiac events were reported as serious adverse events (including atrial fibrillation, myocardial

infarction, left ventricular failure, myocardial ischemia) in 3 % of patients treated with rituximab compared to <1 % on observation. In studies evaluating rituximab in combination with chemotherapy, the incidence of grade 3 and 4 cardiac arrhythmias, predominantly supraventricular arrhythmias such as tachycardia and atrial flutter/fibrillation, was higher in the R-CHOP group (14 patients, 6,9 %) as compared to the CHOP group (3 patients, 1,5 %). All of these arrhythmias either occurred in the context of a rituximab infusion or were associated with predisposing conditions such as fever, infection, acute myocardial infarction or pre-existing respiratory and cardiovascular disease. No difference between the R-CHOP and CHOP group was observed in the incidence of other grade 3 and 4 cardiac events including heart failure, myocardial disease and manifestations of coronary artery disease. In CLL, the overall incidence of grade 3 or 4 cardiac disorders was low both in the first-line study (4 % R-FC, 3 % FC) and in the relapsed/refractory study (4 % R-FC, 4 % FC).

Respiratory system

Cases of interstitial lung disease, some with fatal outcome have been reported.

Neurologic events

During the treatment period, four patients (2 %) treated with R-CHOP, all with cardiovascular risk factors, experienced thromboembolic cerebrovascular accidents during the first treatment cycle. There was no difference between the treatment groups in the incidence of other thromboembolic events. In contrast, three patients (1,5 %) had cerebrovascular events in the CHOP group, all of which occurred during the follow-up period. In CLL, the overall incidence of grade 3 or 4 nervous system disorders was low both in the first-line study (4 % R-FC,4 % FC) and in the relapsed/refractory study (3 % RFC, 3 % FC).

Cases of posterior reversible encephalopathy syndrome (PRES) / reversible posterior leukoencephalopathy syndrome (RPLS) have been reported. Signs and symptoms included visual disturbance, headache, seizures and altered mental status, with or without associated hypertension.

A diagnosis of PRES/RPLS requires confirmation by brain imaging. The reported cases had recognized risk factors for PRES/RPLS, including the patients' underlying disease, hypertension, immunosuppressive therapy and/or chemotherapy.

Gastrointestinal Disorders

Gastrointestinal perforation in some cases leading to death has been observed in patients receiving rituximab for treatment of non Hodgkin lymphoma. In the majority of these cases, rituximab was administered with chemotherapy.

IgG levels

In the clinical trial evaluating rituximab maintenance treatment, median IgG levels were below the lower limit of normal (LLN) (< 7 g/L) after induction treatment in both the observation and the rituximab groups. In the observation group, the median IgG level subsequently increased to above the LLN, but remained constant in the rituximab group. The proportion of patients with IgG levels below the LLN was about 60 % in the rituximab group throughout the 2-year treatment period, while it decreased in the observation group (36 % after 2 years).

A small number of spontaneous and literature cases of hypogammaglobulinaemia have been observed in paediatric patients treated with rituximab, in some cases severe and requiring long-term immunoglobulin substitution therapy. The consequences of long-term B cell depletion in paediatric patients are unknown.

Skin and subcutaneous tissue disorders:

Toxic Epidermal Necrolysis (Lyell syndrome) and Stevens-Johnson syndrome, some with fatal outcome, have been reported very rarely.

Patient subpopulations -Rituximab monotherapy

Elderly patients (= 65 years):

The incidence of ADRs of all grades and grade 3 /4 ADR was similar in elderly patients compared to younger patients (< 65 years).

Bulky disease:

There was a higher incidence of grade 3/4 ADRs in patients with bulky disease than in patients without bulky disease (25,6 % vs. 15,4 %). The incidence of ADRs of any grade was similar in these two groups.

Re-treatment:

The percentage of patients reporting ADRs upon re-treatment with further courses of rituximab was similar to the percentage of patients reporting ADRs upon initial exposure (any grade and grade 3/4 ADRs).

Patient subpopulations - Rituximab combination therapy

Elderly patients (= 65 years)

The incidence of grade 3/4 blood and lymphatic adverse events was higher in elderly patients compared to younger patients (< 65 years), with previously untreated or relapsed/refractory CLL.

Experience from granulomatosis with polyangiitis and microscopic polyangiitis

Induction of remission

99 patients were treated for induction of remission of GPA and MPA in an innovator's clinical trial, with rituximab (375 mg/m^2 once weekly for 4 weeks) and glucocorticoids.

The ADRs listed in Table 2 were all adverse events which occurred at an incidence of = 5 % in the rituximab group and at a higher frequency than the comparator group.

Table 2 Adverse drug reactions occurring at 6-months in ≥ 5 % of patients receiving rituximab for induction of remission of GPA and MPA, and at a higher frequency than the comparator group.

MedDRA System Organ Class ***Adverse Event***	***Rituximab*** ***(n=99)***
Infections and infestations	
Urinary tract infection	7 %
Bronchitis	5 %
Herpes zoster	5 %
Nasopharyngitis	5 %
Blood and lymphatic system disorders	
Thrombocytopenia	7 %
Immune system disorders	
Cytokine release syndrome	5 %
Metabolism and nutrition disorders	
Hyperkalaemia	5 %
Psychiatric disorders	
Insomnia	14 %
Nervous system disorders	

Dizziness	10 %
Tremor	10 %
Vascular disorders	
Hypertension	12 %
Flushing	5 %
Respiratory, thoracic and mediastinal disorders	
Cough	12 %
Dyspnoea	11 %
Epistaxis	11 %
Nasal congestion	6 %
Gastrointestinal disorders	
Diarrhoea	18 %
Dyspepsia	6 %
Constipation	5 %
Skin and subcutaneous tissue disorders	
Acne	7 %
Musculoskeletal and connective tissue disorders	
Muscle spasms	18 %
Arthralgia	15 %
Back pain	10 %
Muscle weakness	5 %
Musculoskeletal pain	5 %
Pain in extremities	5 %
Investigations	
General disorders and administration site conditions	
Peripheral oedema	16 %
Investigations	
Decreased haemoglobin	6 %

Maintenance treatment

In a further clinical study, a total of 57 severe, active GPA and MPA patients in disease remission were treated with rituximab for the maintenance of remission.

Table 3 Adverse drug reactions occurring in ≥ 5 % of patients receiving rituximab for maintenance treatment of GPA and MPA, and at a higher frequency than the comparator group

MedDRA System organ class Adverse reaction	Rituximab (n=57)
Infections and infestations	
Bronchitis	14 %
Rhinitis	5 %
Respiratory, thoracic and mediastinal disorders	
Dyspnoea	9 %
Gastrointestinal disorders	
Diarrhoea	7 %
General disorders and administration site conditions	
Pyrexia	9 %
Influenza-like illness	5 %
Oedema peripheral	5 %
Injury, poisoning and procedural complications	
Infusion-related reactions[1]	12 %
[1] Details on infusion related reactions are provided in the description of selected adverse drug reactions section.	

The overall safety profile was consistent with the well-established safety profile for rituximab in approved autoimmune indications, including GPA/MPA. Overall, 4 % of patients in the rituximab arm experienced adverse events leading to discontinuation. Most adverse events in the rituximab arm were mild or moderate in intensity. No patients in the rituximab arm had fatal adverse events. The most commonly reported events considered as ADRs were infusion-related reactions and infections.

In a long-term observational safety study, 97 GPA/MPA patients received treatment with rituximab (mean of 8 infusions [range 1 to 28]) for up to 4 years, according to their physician's standard practice and discretion. The overall safety profile was consistent with the well-established safety profile of rituximab in GPA/MPA and no new adverse drug reactions were reported.

Description of selected adverse drug reactions

Infusion-related reactions

In the clinical trial conducted by innovator studying induction of remission with severe active GPA and MPA, IRRs were defined as any adverse event occurring within 24 hours of an infusion and considered to be infusion-related by investigators in the safety population. Of the 99 patients treated with rituximab, 12 (12 %) experienced at least one IRR. All IRRs were CTC Grade 1 or 2. The most common IRRs included cytokine release syndrome, flushing, throat irritation, and tremor. Rituximab was given in combination with intravenous glucocorticoids which may reduce the incidence and severity of these events.

In the maintenance therapy clinical trial, 7/57 (12 %) patients in the rituximab arm experienced at least one infusion-related reaction. The incidence of IRR symptoms was highest during or after the first infusion (9 %) and decreased with subsequent infusions (< 4 %). All IRR symptoms were mild

or moderate and most of them were reported from the SOCs Respiratory, Thoracic and Mediastinal Disorders and Skin and Subcutaneous Tissue disorders.

Infections

In the clinical trial on induction of remission, which included 99 rituximab-treated patients, the overall rate of infection was approximately 237 per 100 patient years (95 % CI 197 to 285) at the 6-month primary endpoint. Infections were predominately mild to moderate and consisted mostly of upper respiratory tract infections, herpes zoster and urinary tract infections. The rate of serious infections was approximately 25 per 100 patient years. The most frequently reported serious infection in the rituximab group was pneumonia at a frequency of 4 %.

In the maintenance therapy clinical trial, 30/57 (53 %) patients in the rituximab arm experienced infections. The incidence of all grade infections was similar between the arms. Infections were predominately mild to moderate. The most common infections in the rituximab arm included upper respiratory tract infections, gastroenteritis, urinary tract infections and herpes zoster. The incidence of serious infections was similar in both arms (approximately 12 %). The most commonly reported serious infection in the rituximab group was mild or moderate bronchitis.

Malignancies

In the clinical trial on induction of remission, the incidence of malignancy in rituximab treated patients in the granulomatosis with polyangiitis and microscopic polyangiitis clinical study was 2,00 per 100 patient years at the study common closing date (when the final patient had completed the follow-up period). On the basis of standardised incidence ratios, the incidence of malignancies appears to be similar to that previously reported in patients with ANCA-associated vasculitis.

Cardiovascular adverse reactions

In the clinical trial on induction of remission, cardiac events occurred at a rate of approximately 273 per 100 patient years (95 % CI 149 to 470) at the 6-month primary endpoint. The rate of serious cardiac events was 2.1 per 100 patient years (95 % CI 3 to 15). The most frequently reported events were tachycardia (4 %) and atrial fibrillation (3 %).

Neurologic events

Cases of posterior reversible encephalopathy syndrome (PRES)/reversible posterior leukoencephalopathy syndrome (RPLS) have been reported in autoimmune conditions. Signs and symptoms included visual disturbance, headache, seizures and altered mental status, with or without associated hypertension. A diagnosis of PRES/RPLS requires confirmation by brain imaging. The reported cases had recognised risk factors for PRES/RPLS, including the patients' underlying disease, hypertension, immunosuppressive therapy and/or chemotherapy.

Hepatitis-B reactivation

A small number of cases of hepatitis-B reactivation, some with fatal outcome, have been reported in granulomatosis with polyangiitis and microscopic polyangiitis patients receiving rituximab in the post marketing setting.

Hypogammaglobulinaemia

Hypogammaglobulinaemia (IgA, IgG or IgM below the lower limit of normal) has been observed in granulomatosis with polyangiitis and microscopic polyangiitis patients treated with rituximab. The rate of overall infections and serious infections was not increased after the development of low IgA, IgG or IgM.

In the induction of remission clinical trial, at 6 months, in the rituximab group, 27 %, 58 % and 51 % of patients with normal immunoglobulin levels at baseline had low IgA, IgG and IgM levels, respectively, compared to 25 %, 50 % and 46 % in the cyclophosphamide group.
In the maintenance therapy clinical trial, no clinically meaningful differences between the two treatment arms or decreases in total immunoglobulin, IgG, IgM or IgA levels were observed throughout the trial.

Neutropenia
In the induction of remission clinical trial, 24 % of patients in the rituximab group (single course) and 23 % of patients in the cyclophosphamide group developed CTC grade 3 or greater neutropenia. Neutropenia was not associated with an observed increase in serious infection in rituximab-treated patients.
In the maintenance therapy clinical trial, the incidence of all-grade neutropenia was 0 % for Rituximab-treated patients vs. 5 % for azathioprine treated patients.

Skin and subcutaneous tissue disorders
Toxic Epidermal Necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome, some with fatal outcome, have been reported very rarely.

Experience from pemphigus vulgaris
Summary of the safety profile
The safety profile of rituximab in combination with short-term, low-dose glucocorticoids in the treatment of patients with pemphigus vulgaris was studied in an innovator’s Phase 3, randomised, controlled, multicenter, open-label study in pemphigus patients that included 38 pemphigus vulgaris (PV) patients randomised to the Rituximab group. Patients randomised to the Rituximab

group received an initial 1000 mg IV on Study Day 1 and a second 1000 mg IV on Study Day 15. Maintenance doses of 500 mg IV were administered at months 12 and 18. Patients could receive 1000 mg IV at the time of relapse.

The safety profile of Rituximab in patients with PV was consistent with that observed in GPA/MPA patients.

Tabulated list of adverse reactions

Adverse drug reactions presented in Table 4 were adverse events which occurred at a rate of ≥ 5 % among Rituximab-treated PV patients, with a ≥ 2 % absolute difference in incidence between the Rituximab-treated group and the standard-dose prednisone group up to month 24. No patients were withdrawn due to ADRs.

Table 4 Adverse drugs reactions for Rituximab-treated pemphigus vulgaris patients in the clinical study up to month 24

System Organ Class Adverse drug reaction	**Rituximab + low-dose prednisone** **(n = 38)**
Injury, Poisoning and Procedural Complications	
Infusion-related reactions*	58 %
Skin and Subcutaneous Tissue Disorders	
Alopecia	13 %
Pruritus	5 %
Urticaria	5 %
Skin disorder	5 %
Psychiatric Disorders	
Persistent depressive disorder	13 %
Major depression	5 %

Irritability	5 %
Infections and Infestations	
Herpes virus infection	8 %
Herpes zoster	5 %
Oral herpes	5 %
Conjunctivitis	5 %
General Disorders and Administration Site Conditions	
Fatigue	8 %
Pyrexia	5 %
Nervous System Disorders	
Headache	5 %
Dizziness	5 %
Gastrointestinal Disorders	
Abdominal pain upper	5 %
Cardiac Disorders	
Tachycardia	5 %
Musculoskeletal and Connective Tissue Disorders	
Musculoskeletal pain	5 %
Neoplasms Benign, Malignant and Unspecified (incl. cysts and polyps)	
Skin papilloma	5 %
* Infusion-related reactions included symptoms collected on the next scheduled visit after each infusion, and adverse events occurring on the day of or one day after the infusion. The most common infusion-related reaction symptoms/Preferred Terms included headaches, chills, high blood pressure, nausea, asthenia and pain.	

Description of selected adverse reactions

Infusion-related reactions

Infusion-related reactions in the pemphigus vulgaris clinical study were common (58 %). Nearly all infusion-related reactions were mild to moderate. The proportion of patients experiencing an infusion- related reaction was 29 % (11 patients), 40 % (15 patients), 13 % (5 patients), and 10 % (4 patients) following the first, second, third, and fourth infusions, respectively. No patients were withdrawn from treatment due to infusion-related reactions. Symptoms of infusion-related reactions were similar in type and severity to those seen in GPA/MPA patients.

Infections

Fourteen patients (37 %) in the Rituximab group experienced treatment-related infections compared to 15 patients (42 %) in the standard-dose prednisone group. The most common infections in the Rituximab group were herpes simplex and zoster infections, bronchitis, urinary tract infection, fungal infection and conjunctivitis. Three patients (8 %) in the Rituximab group experienced a total of 5 serious infections (Pneumocystis jirovecii pneumonia, infective thrombosis, intervertebral discitis, lung infection, Staphylococcal sepsis) and one patient (3 %) in the standard-dose prednisone group experienced a serious infection (Pneumocystis jirovecii pneumonia).

Post-marketing experience

Non Hodgkin Lymphoma (NHL) and Chronic Lymphocytic Leukaemia (CLL):

The reporting frequencies in this section are based on estimated marketed exposures and largely data derived from spontaneous reports.

As part of the continuing post-marketing surveillance of rituximab safety, the following severe adverse reactions have been observed:

Infusion-related reactions

Additional cases of severe infusion-related reactions have been reported during post-marketing use of rituximab.

Cardiovascular system

Severe cardiac events, including heart failure and myocardial infarction have been observed mainly in patients with prior cardiac condition and/or cardiotoxic chemotherapy and mostly associated with infusion related reactions. Vasculitis, predominantly cutaneous, such as leukocytoclastic vasculitis, has been reported.

Respiratory system

Respiratory failure/insufficiency, lung infiltration in the context of infusion-related reactions (see Section 4.4). In addition to pulmonary events associated with infusions, interstitial ling disease, some with fatal outcome, has been reported.

Blood and lymphatic system

Cases of infusion-related acute reversible thrombocytopenia have been reported.

Skin and Appendages

Severe bullous skin reactions including fatal cases of toxic epidermal necrolysis have been reported.

Nervous system

Cases of posterior reversible encephalopathy syndrome (PRES)/reversible posterior leuko-encephalopathy syndrome (RPLS) have been reported. Signs and symptoms include visual disturbance, headache, seizures and altered mental status, with or without associated

hypertension. A diagnosis of PRES/RPLS requires confirmation by brain imaging. The reported cases had recognised risk factors for PRES/RPLS such as patients underlying disease, hypertension, immunosuppressive therapy and/or chemotherapy.
Cases of cranial neuropathy with or without peripheral neuropathy have been reported rarely. Signs and symptoms of cranial neuropathy, such as severe vision loss, hearing loss, loss of other senses, facial nerve palsy occurred at various times up to several months after completion of rituximab therapy.

Body as a whole

Serum sickness-like reactions have been reported rarely.

Infections and infestations:

Cases of hepatitis B reactivation have been reported, the majority of which were in subjects receiving rituximab in combination with cytotoxic chemotherapy (see Section 4.4).
Other serious viral infections (e.g., viral infections are infection caused by the herpes viruses (cytomegalovirus (CMV), Varicella zoster virus and Herpes simplex virus), JC virus (progressive multifocal leukoencephalopathy (PML) and Hepatitis C virus), either new, reactivation or exacerbation, some of which were fatal, have been reported with rituximab in treatment. The majority of the patients had received rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant.

Progression of Kaposi's sarcoma has been observed in rituximab -exposed patients with pre-existing Kaposi's sarcoma. These cases occurred in non-approved indications and the majority of the patients were HIV positive.

Gastro-intestinal system

Gastro-intestinal perforation, in some cases leading to death, has been observed in patients receiving rituximab in combination with chemotherapy or non Hodgkin lymphoma.

Laboratory Abnormalities

Non Hodgkin Lymphoma

Blood and lymphatic system:

Neutropenia: The onset of neutropenia has occurred more than four weeks after the last infusion of rituximab.

Table 3: Adverse reactions in rituximab-treated pemphigus vulgaris patients in PV Study 1 (up to Month 24) and PV Study 2 (up to Week 52)

System Organ Class	Frequent
Infections and infestations	Upper respiratory tract infection, Herpes virus infection, Herpes zoster, oral herpes, conjunctivitis, nasopharyngitis oral candidiasis, Urinary tract infection
Neoplasms Benign, Malignant and Unspecified (incl	Skin papilloma
Psychiatric disorders	Persistent depressive disorder, major depression, irritability
Nervous system disorders	Headache, dizziness
Cardiac disorders	Tachycardia
Gastrointestinal disorders	Upper abdominal pain

Skin and subcutaneous tissue disorders	Alopecia, pruritus, urticaria, skin disorder
Musculoskeletal, connective tissue and bone disorders	Musculoskeletal pain, arthralgia, back pain
General disorders and administration site conditions	Fatigue, asthenia, pyrexia
Injury, Poisoning and Procedural Complications	Infusion-related reactions*
*Infusion-related reactions for PV Study 1 included symptoms collected on the next scheduled visit after each infusion, and adverse events occurring on the day of or one day after the infusion. The most common infusion-related reaction symptoms/Preferred Terms for PV Study 1 included headaches, chills, high blood pressure, nausea, asthenia and pain. The most frequent infusion-related reaction symptoms/Preferred Terms for PV Study 2 were dyspnoea, erythema, hyperhidrosis,	

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

Suspected adverse reactions can also be reported directly to the HCR via the link https://pvi1j.solutions.iqvia.com or the e-mail address, adverse.event.sac@sandoz.com.

4.9 Overdose

Limited experience with doses higher than the approved dose of intravenous rituximab formulation is available from clinical trials in humans. The highest intravenous dose of rituximab tested in humans to date is 5000 mg (2250 mg/m^2), tested in a dose escalation study in patients with CLL. No additional safety signals were identified.

Patients who experience overdose should have immediate interruption of their infusion and be closely monitored.

In the post-marketing setting five cases of rituximab overdose have been reported. Three cases had no reported adverse event. The two adverse events that were reported were flu-like symptoms, with a dose of 1.8 g of rituximab and fatal respiratory failure, with a dose of 2 g of rituximab.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties:

Pharmacotherapeutic group: antineoplastic agents, monoclonal antibodies. ATC code: L01X C02

Rituximab binds specifically to the transmembrane antigen, CD20, a non-glycosylated phosphoprotein, located on pre-B and mature B lymphocytes. The antigen is expressed on > 95 % of all B cell non-Hodgkin's lymphomas.

CD20 is found on both normal and malignant B cells, but not on haematopoietic stem cells, pro-B cells, normal plasma cells or other normal tissue. This antigen does not internalise upon antibody binding and is not shed from the cell surface. CD20 does not circulate in the plasma as a free antigen and, thus, does not compete for antibody binding.

The Fab domain of rituximab binds to the CD20 antigen on B lymphocytes and the Fc domain can recruit immune effector functions to mediate B cell lysis. Possible mechanisms of effector-mediated cell lysis include complement-dependent cytotoxicity (CDC) resulting from C1q binding, and antibody-dependent cellular cytotoxicity (ADCC) mediated by one or more of the Fcγ receptors on the surface of granulocytes, macrophages and NK cells. Rituximab binding to CD 20 antigen on B lymphocytes has also been demonstrated to induce cell death via apoptosis.

Peripheral B cell counts declined below normal following completion of the first dose of rituximab. In patients treated for haematological malignancies, B cell recovery began within 6 months of treatment and generally returned to normal levels within 12 months after completion of therapy, although in some patients this may take longer (up to a median recovery time of 23 months post-induction therapy). Peripheral blood B cell counts begin to increase from week 24 and evidence for repopulation is observed in the majority of patients by week 40, whether rituximab was administered as monotherapy or in combination with methotrexate. A small proportion of patients had prolonged peripheral B cell depletion lasting 2 years or more after their last dose of rituximab. In patients with GPA or MPA, the number of peripheral blood B cells decreased to <10 cells/µl after two weekly infusions of rituximab 375 mg/m^2 and remained at that level in most patients up to the 6 month time point. The majority of patients (81 %) showed signs of B cell return, with counts >10 cells/µl by month 12, increasing to 87 % of patients by month 18.

5.2 Pharmacokinetic properties

Adult Non-Hodgkin's lymphoma:

Based on a population pharmacokinetic analysis in 298 NHL patients who received single or multiple infusions of rituximab as a single agent or in combination with CHOP therapy (applied rituximab doses ranged from 100 to 500 mg/m^2), the typical population estimates of nonspecific clearance (CL_1), specific clearance (CL_2) likely contributed by B cells or tumour burden, and central compartment volume of distribution (V_1) were 0,14 L/day, 0,59 L/day, and 2,7 L, respectively. The

estimated median terminal elimination half-life of rituximab was 22 days (range, 6,1 to 52 days). Baseline CD19-positive cell counts and size of measurable tumour lesions contributed to some of the variability in CL_2 of rituximab in data from 161 patients given 375 mg/m^2 as an intravenous infusion for 4 weekly doses. Patients with higher CD19-positive cell counts or tumour lesions had a higher CL_2. However, a large component of inter-individual variability remained for CL_2 after correction for CD19-positive cell counts and tumour lesion size. V_1 varied by body surface area (BSA) and CHOP therapy. This variability in V_1 (27,1 % and 19,0 %) contributed by the range in BSA (1,53 to 2,32 m^2) and concurrent CHOP therapy, respectively, were relatively small. Age, gender and WHO performance status had no effect on the pharmacokinetics of rituximab. This analysis suggests that dose adjustment of rituximab with any of the tested covariates is not expected to result in a meaningful reduction in its pharmacokinetic variability.

Rituximab, administered as an intravenous infusion at a dose of 375 mg/m^2 at weekly intervals for 4 doses to 203 patients with NHL naive to rituximab, yielded a mean C_{max} following the fourth infusion of 486 µg/mL (range, 77,5 to 996,6 µg/mL). Rituximab was detectable in the serum of patients 3 – 6 months after completion of last treatment.

Upon administration of rituximab at a dose of 375 mg/m^2 as an intravenous infusion at weekly intervals for 8 doses to 37 patients with NHL, the mean C_{max} increased with each successive infusion, spanning from a mean of 243 µg/mL (range, 16 – 582 µg/mL) after the first infusion to 550 µg/mL (range, 171 – 1177 µg/mL) after the eighth infusion.

The pharmacokinetic profile of rituximab when administered as 6 infusions of 375 mg/m^2 in combination with 6 cycles of CHOP chemotherapy was similar to that seen with rituximab alone.

Paediatric DLBCL/BL/BAL/BLL:

In the clinical trial studying paediatric DLBCL/BL/BAL/BLL, the PK was studied in a subset of 35 patients aged 3 years and older. The PK was comparable between the two age groups (≥3 to <12

years vs. ≥12 to <18 years). After two rituximab IV infusions of 375 mg/m^2 in each of the two induction cycles (cycle 1 and 2) followed by one rituximab IV
infusion of 375 mg/m^2 in each of the consolidation cycles (cycle 3 and 4) the maximum concentration was highest after the fourth infusion (cycle 2) with a geometric mean of 347 g/Ml followed by lower geometric mean maximum concentrations thereafter (Cycle 4: 247 g/Ml). With this dose regimen, trough levels were sustained (geometric means: 41,8 µg/Ml (pre-dose Cycle 2; after 1 cycle), 67,7 µg/Ml (pre-dose Cycle 3, after 2 cycles) and 58,5 µg/Ml (pre-dose Cycle 4, after 3 cycles)). The median elimination half-life in paediatric patients aged 3 years and older was 26 days.

The PK characteristics of rituximab in paediatric patients with DLBCL/BL/BAL/BLL were similar to what has been observed in adult NHL patients.

No PK data are available in the ≥ 6 months to < 3 years age group, however, population PK prediction supports comparable systemic exposure (AUC, C_{trough}) in this age group compared to ≥ 3 years (Table 24). Smaller baseline tumor size is related to higher exposure due to lower time dependent clearance, however, systemic exposures impacted by different tumor sizes remain in the range of exposure that was efficacious and had an acceptable safety profile.

Table 24: Predicted PK Parameters following the Rituximab Dosing Regimen in Paediatric DLBCL/BL/BAL/BLL

Age group	≥ 6 mo to < 3 years	≥ 3 to < 12 years	≥ 12 to < 18 years
C_{trough} (µg/mL)	47.5 (0.01-179)	51.4 (0.00-182)	44.1 (0.00-149)
$AUC_{1\text{-}4\ cycles}$ (µg*day/mL)	13501 (278-31070)	11609 (135-31157)	11467 (110-27066)

Results are presented as median (min – max); C_{trough} is pre-dose Cycle 4.

Chronic lymphocytic leukaemia:

Rituximab was administered as an intravenous infusion at a first-cycle dose of 375 mg/m^2 increased to 500 mg/m^2 each cycle for 5 doses in combination with fludarabine and

cyclophosphamide in CLL patients. The mean C_{max} (N=15) was 408 µg/mL (range, 97 – 764 µg/mL) after the fifth 500 mg/m^2 infusion and the mean terminal half-life was 32 days (range, 14 – 62 days).

Granulomatosis with polyangiitis and microscopic polyangiitis

Based on the population pharmacokinetic analysis of data in 97 GPA and MPA patients who received 375 mg/ m^2 rituximab once a week for 4 doses, the estimated median terminal elimination half-life was 23 days (range 9 to 49 days). Rituximab mean clearance and volume of distribution were 0,313 L/day (range of 0,116 to 0,726 L/day) and 4,50 L (range of 2,25 to 7,39 L) respectively.

5.3 Preclinical safety data

Rituximab has shown to be highly specific to the CD20 antigen on B cells. Toxicity studies in cynomolgus monkeys have shown no other effect than the expected pharmacological depletion of B cells in peripheral blood and in lymphoid tissue.

Developmental toxicity studies have been performed in cynomolgus monkeys at doses up to 100 mg/kg (treatment on gestation days 20-50) and have revealed no evidence of toxicity to the foetus due to rituximab. However, dose dependent pharmacologic depletion of B cells in the lymphoid organs of the foetuses was observed, which persisted post natally and was accompanied by a decrease in IgG level in the newborn animals affected. B cell counts returned to normal in these animals within 6 months of birth and did not compromise the reaction to immunisation.

Standard tests to investigate mutagenicity have not been carried out, since such tests are not relevant for this molecule.

No long-term animal studies have been performed to establish the carcinogenic potential of rituximab.

Specific studies to determine the effects of rituximab on fertility have not been performed. In general toxicity studies in cynomolgus monkeys no deleterious effects on reproductive organs in males or females were observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate

Polysorbate 80

Sodium chloride

Sodium hydroxide (for pH adjustment)

Hydrochloric acid (for pH adjustment)

Water for Injection

6.2 Incompatibilities

No incompatibilities between RIXATHON and Polyvinylidene difluoride or Polyethersulfone bags or infusion sets have been observed.

6.3 Shelf life

3 years

After first opening: the solution for injection is for single use only. Unused solution must be discarded.

6.4 Special precautions for storage

Store in a refrigerator at 5 ± 3 °C.

RIXATHON is stable for up to five cycles of freezing at ≤ - 20 °C and thawing at 5 ± 3 °C for at least 12 hours.

In-use:

0.9 % NaCl i.v. solution is suitable for compounding and storage for 30 days at 5 ± 3 °C

5 % glucose i.v. solution is only regarded suitable for short-term up to 40 hours (24 hours at 5 ± 3 °C plus 16 hours at room temperature).

Store in the original packaging.

Keep the vials in the carton until required for use.

Keep the vial well closed.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

RIXATHON 100 mg/10 mL is filled in a clear, colorless vial made of tubular glass (hydrolytic class I, according to Ph. Eur. & USP) and closed with blow back rubber stoppers.

The vial stopper combination is crimped with an aluminum cap with a flip off component coloured in “ivory”.

RIXATHON 500 mg/50 mL is filled in a clear, colorless vial made of tubular glass (hydrolytic class I, according to Ph. Eur. & USP) and closed with blow back rubber stoppers.

The vial stopper combination is crimped with an aluminum cap with a flip off component coloured in “blue”.

Pack sizes:

2 x 10 mL ampoules per pack

1 x 50 mL ampoules per pack

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Withdraw the required amount of RIXATHON under aseptic conditions and dilute to a calculated rituximab concentration of 1 – 4 mg/mL in an infusion bag containing sterile, non-pyrogenic 0,9 % normal saline solution or 5 % dextrose solution (D5W) for infusion. To mix the solution, gently invert the bag to avoid foaming. Parenteral medications should be inspected visually for particulate matter or discolouration prior to administration.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1]

Waterfall 5-Ir

Magwa Crescent West

Waterfall City

Jukskei View

2090

8. REGISTRATION NUMBERS

RIXATHON 100 mg/10 ml: 55/26/0405

RIXATHON 500 mg/50 ml: 55/26/0406

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 March 2024

10. DATE OF REVISION OF THE TEXT

Not applicable.

[1]Company Reg. No.: 1990/001979/07