

1. NAME OF THE MEDICINAL PRODUCT

Rixathon Concentrate for Solution for Infusion 100mg/10ml

Rixathon Concentrate for Solution for Infusion 500mg/50ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

100mg/10ml

Each 10 mL vial contains 100 mg of rituximab.

500mg/50ml

Each 50 mL vial contains 500 mg of rituximab.

Rituximab is a genetically engineered chimeric mouse/human monoclonal antibody representing a glycosylated immunoglobulin with human IgG1 constant regions and murine light-chain and heavy-chain variable region sequences. The antibody is produced by mammalian (Chinese hamster ovary) cell suspension culture and purified by affinity chromatography and ion exchange, including specific viral inactivation and removal procedures.

Rixathon is a biosimilar medicine to the reference product MabThera.

Excipient with known effect

Each 10 mL vial contains 2.3 mmol (52.6 mg) sodium.

Each 50 mL vial contains 11.5 mmol (263.2 mg) sodium.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear, colourless to slightly yellowish liquid with pH of 6.3 – 6.7 and osmolality of ≥ 240 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Non-Hodgkin's Lymphoma

Rixathon is indicated for the treatment of:

- patients with relapsed or chemoresistant 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 CD20-positive diffuse large B-cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) chemotherapy.

Chronic Lymphocytic Leukemia (CLL)

Rixathon is indicated, in combination with chemotherapy, for the treatment of patients with previously untreated and relapsed/refractory CD20-positive Chronic Lymphocytic Leukemia.

Granulomatosis with Polyangiitis (Wegener's) (GPA) and Microscopic Polyangiitis (MPA)

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

4.2 Posology and method of administration

General

Substitution by any other biological medicinal product requires the consent of the prescribing physician.

It is important to check the product labels to ensure that the appropriate formulation (IV or SC) and strength is being given to the patient, as prescribed.

Rixathon should always be administered in an environment where full resuscitation facilities are immediately available, and under the close supervision of an experienced physician.

Premedication and Prophylactic Medications

Premedication consisting of an analgesic/anti-pyretic (e.g., paracetamol/acetaminophen) and an anti-histaminic drug (e.g., diphenhydramine) should always be given before each administration of Rixathon. Premedication with glucocorticoids should also be considered, particularly if Rixathon is not given in combination with steroid-containing chemotherapy (see section 4.4).

In adult patients with non-Hodgkin's lymphoma and CLL, premedication with glucocorticoids should be considered if Rixathon is not given in combination with glucocorticoid-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 $> 25 \times 10^9/L$ it is recommended to administer prednisone/prednisolone 100 mg intravenously shortly before infusion with Rixathon to decrease the rate and severity of acute infusion reactions and/or cytokine release syndrome.

In patients with GPA or MPA or pemphigus vulgaris, premedication with 100 mg intravenous methylprednisolone should be completed 30 minutes prior to each infusion of Rixathon to decrease the incidence and severity of infusion related reactions (IRRs).

In adult patients with GPA or MPA, 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.

Dosage adjustments during treatment:

No dose reductions of Rixathon are recommended. When Rixathon is given in combination with chemotherapy, standard dose reductions for the chemotherapeutic drugs should be applied.

Rixathon IV formulation is not intended for subcutaneous administration.

Do not administer the prepared infusion solutions as a push or bolus (see section 6.6).

Intravenous Formulation Infusion Rate

First intravenous infusion:

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

Subsequent intravenous infusions:

Subsequent infusions of Rixathon can be started at a rate of 100 mg/hour and increased by 100 mg/hour increments every 30 minutes to a maximum of 400 mg/hour.

Standard dosage

Low-grade or follicular non-Hodgkin's lymphoma

Initial treatment

- Intravenous monotherapy

The recommended dosage of Rixathon used as monotherapy for adult patients is 375 mg/m² body surface area (BSA), administered as an intravenous infusion (see "Intravenous Formulation Infusion Rate" sub-section, above) once weekly for 4 weeks.

The recommended dosage of Rixathon IV (R-IV) in combination with any chemotherapy is 375 mg/m² body surface area per cycle for a total of:

- 8 cycles R-IV with CVP (21 days/cycle)
- 8 cycles R-IV with MCP (28 days/cycle)
- 8 cycles R-IV with CHOP (21 days/cycle); 6 cycles if a complete remission is achieved after 4 cycles
- 6 cycles with R-CHVP-Interferon (21 days/cycle)

Rixathon should be administered on day 1 of each chemotherapy cycle after intravenous administration of the glucocorticoid component of the chemotherapy, if applicable.

Re-treatment following relapse

Patients who have responded to Rixathon initially may receive Rixathon at a dose of 375 mg/m² BSA, administered as an i.v. infusion once weekly for 4 weeks.

Maintenance treatment

Previously untreated patients after response to induction treatment may receive maintenance therapy with Rixathon given at 375mg/m² once every 2 months until disease progression or for a maximum period of two years (12 infusions in total).

Relapsed/refractory patients after response induction treatment may receive maintenance therapy with Rixathon given at 375 mg/m² once every 3 months until disease progression or for a maximum period of two years (8 infusions in total).

Diffuse large B-cell non-Hodgkin's lymphoma

In patients with diffuse large B cell non-Hodgkin's lymphoma Rixathon should be used in combination with CHOP (cyclophosphamide, doxorubicin, prednisone and vincristine) chemotherapy. The recommended dosage of Rixathon is 375 mg/m² BSA, administered on day 1 of each chemotherapy cycle for 8 cycles after i.v. administration of the glucocorticoid component of CHOP (see "Intravenous Formulation Infusion Rate" sub-section, above).

Chronic Lymphocytic Leukemia

The recommended dosage of Rixathon in combination with chemotherapy for previously untreated and relapsed/refractory CLL patients is 375 mg/m² BSA administered on day 1 of the first treatment cycle followed by 500 mg/m² BSA administered on day 1 of each subsequent cycle for 6 cycles in total. The chemotherapy should be given after the Rixathon infusion (see "Intravenous Formulation Infusion Rate" subsection, above).

Adult patients - Non-Hodgkin's lymphoma (NHL) and Chronic lymphocytic leukaemia (CLL) only:

If patients did not experience a Grade 3 or 4 infusion-related adverse event during Cycle 1, a 90-minute infusion can be administered in Cycle 2 with a glucocorticoid-containing chemotherapy regimen. Initiate at a rate of 20% of the total dose given in the first 30 minutes and the remaining 80% of the total dose given over the next 60 minutes. If the 90-minute infusion is tolerated in Cycle 2, the same rate can be used when administering the remainder of the treatment regimen (through Cycle 6 or 8).

Patients who have clinically significant cardiovascular disease, including arrhythmias, or previous serious infusion reactions to any prior biologic therapy or to rituximab, should not be administered the more rapid infusion.

Granulomatosis with polyangiitis (Wegener's) (GPA) and Microscopic polyangiitis (MPA)

The recommended dosage of Rixathon for treatment of GPA and MPA is 375 mg/m² BSA, administered as an IV infusion (see "Intravenous Formulation Infusion Rate" sub-section, above) once weekly for 4 weeks.

Methylprednisolone 1000 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 IV treatment.

Pneumocystis jiroveci pneumonia (PCP) prophylaxis is recommended for patients with GPA and MPA prior to and Rixathon IV treatment, as appropriate according to local clinical practice guidelines.

4.2.2.1 Special Dosage Instructions

Pediatric use:

The safety and efficacy of Rixathon in children and adolescents (<18 years) have not been established.

Geriatric use:

No dose adjustment is required in patients aged ≥ 65 years of age.

4.3 ContraindicationsContraindications for use in non-Hodgkin's lymphoma and chronic lymphocytic leukaemia

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.

Contraindications for use in granulomatosis with polyangiitis, microscopic polyangiitis and pemphigus vulgaris

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 the traceability of biological medicinal products, the trade name and batch number of the administered product should be clearly recorded (or stated) in the patient file.

Progressive multifocal leukoencephalopathy

All patients treated with rituximab for rheumatoid arthritis, 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, cerebro spinal fluid (CSF) testing for JC Viral DNA and repeat neurological assessments, should be considered.

The physician 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 leukaemiaInfusion-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 ($\geq 25 \times 10^9/L$) of circulating malignant cells such as patients with CLL, who may be at higher risk of especially severe cytokine release syndrome, should 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 $>25 \times 10^9/L$.

Infusion-related adverse reactions of all kinds have been observed in 77% of patients treated with rituximab (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 rituximab 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 rituximab.

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

anti-hypertensive 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 rituximab. Therefore patients with a history of cardiac disease and/or cardiotoxic chemotherapy should be monitored closely.

Haematological toxicities

Although rituximab is not myelosuppressive in monotherapy, caution should be exercised when considering treatment of patients with neutrophils $< 1.5 \times 10^9/L$ and/or platelet counts $< 75 \times 10^9/L$ 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 rituximab therapy.

Infections

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

Physicians 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 (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.

Cases of enteroviral meningoencephalitis including fatalities have been reported following use of rituximab.

False negative serologic testing of infections

Due to the risk of false negative serologic testing of infections, alternative diagnostic tools should be considered in case of patients presenting with symptoms indicative of rare infectious disease e.g. West Nile virus and neuroborreliosis.

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 rituximab 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)

Infusion-related reactions

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

Severe IRRs with fatal outcome have been reported in rheumatoid arthritis patients in the post-marketing setting. In rheumatoid arthritis most infusion-related events reported in clinical trials 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 rituximab. 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.

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 rituximab.

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 rituximab and patients closely monitored during administration. Since hypotension may occur during rituximab infusion, consideration should be given to withholding anti-hypertensive medications 12 hours prior to the rituximab infusion.

IRRs in patients with GPA, MPA and pemphigus vulgaris were consistent with those seen for rheumatoid arthritis patients in clinical trials and in the post-marketing setting (see section 4.8).

Cardiac disorders

Angina pectoris, cardiac arrhythmias such as atrial flutter and fibrillation, heart failure and/or myocardial infarction have occurred in patients treated with rituximab. 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 rituximab and the knowledge that B cells play an important role in maintaining normal immune response, patients have an increased risk of infection following rituximab

therapy (see section 5.1). Serious infections, including fatalities, can occur during therapy with rituximab (see section 4.8). Rituximab 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). Physicians 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 rituximab.

Patients reporting signs and symptoms of infection following rituximab therapy should be promptly evaluated and treated appropriately. Before giving a subsequent course of rituximab 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 rituximab for the treatment of rheumatoid arthritis and autoimmune diseases including Systemic Lupus Erythematosus (SLE) and vasculitis.

Cases of enteroviral meningoencephalitis including fatalities have been reported following use of rituximab.

False negative serologic testing of infections

Due to the risk of false negative serologic testing of infections, alternative diagnostic tools should be considered in case of patients presenting with symptoms indicative of rare infectious disease e.g. West Nile virus and neuroborreliosis.

Hepatitis B Infections

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

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.

Late neutropenia

Measure blood neutrophils prior to each course of rituximab, 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 rituximab, treatment should be permanently discontinued.

Immunisation

Physicians 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 rituximab.

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 rituximab 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. In a randomised trial, patients with rheumatoid arthritis treated with rituximab and methotrexate had comparable response rates to tetanus recall antigen (39% vs. 42%), reduced rates to pneumococcal polysaccharide vaccine (43% vs. 82% to at least 2 pneumococcal antibody serotypes),

and KLH neoantigen (47% vs. 93%), when given 6 months after rituximab as compared to patients only receiving methotrexate. Should non-live vaccinations be required whilst receiving rituximab therapy, these should be completed at least 4 weeks prior to commencing the next course of rituximab.

In the overall experience of rituximab repeat treatment over one year in rheumatoid arthritis, the proportions of patients with positive antibody titres against *S. pneumoniae*, influenza, mumps, rubella, varicella and tetanus toxoid were generally similar to the proportions at baseline.

Malignancy

Immunomodulatory drugs may increase the risk of malignancy. However, available data do not suggest an increased risk of malignancy for rituximab used in autoimmune indications beyond the malignancy risk already associated with the underlying autoimmune condition.

Excipients

This medicinal product contains 2.3 mmol (or 52.6 mg) sodium per 10 mL vial and 11.5 mmol (or 263.2 mg) sodium per 50 mL vial, equivalent to 2.6% (for 10mL vial) and 13.2% (for 50mL vial) of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

At present, 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 human anti-chimeric antibody (HACA) titers may develop 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 rituximab.

Pregnancy

IgG immunoglobulins are known to cross the placental barrier.

B cell levels in human neonates following maternal exposure to rituximab 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 rituximab during pregnancy. For these reasons rituximab should not be administered to pregnant women unless the possible benefit outweighs the potential risk.

Breast-feeding

Limited data on rituximab excretion into breast milk suggest very low milk levels (relative infant dose less than 0.4%). Few cases of follow-up of breastfed infants describe normal growth and development up to 2 years. However, as these data are limited and the long-term outcomes of breastfed infants remain unknown, breastfeeding is not recommended while being treated with rituximab and optimally for 6 months following rituximab 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 effect of rituximab on the ability to drive and use machines have been performed although the pharmacological activity and adverse events reported to date do not indicate that such an effect is likely.

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 chronic lymphocytic leukaemia 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)
- Infections
- Cardiovascular events

Other serious ADRs reported include hepatitis B reactivation and PML.

List of adverse reactions

The frequencies of ADRs reported with rituximab alone or in combination with chemotherapy are summarised below. Frequencies are defined as very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$) and very rare ($< 1/10,000$) and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in the order of decreasing seriousness.

The ADRs identified only during post-marketing surveillance, and for which a frequency could not be estimated, are listed under "not known".

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.

MedDRA System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	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 Pneumocystis jirovecii	PML	enteroviral meningoencephalitis ^{2, 3}
Blood and lymphatic system disorders	Neutropenia, leucopenia, *febrile neutropenia, *thrombocytopenia	Anaemia, *pancytopenia, *granulocytopenia	Coagulation disorders, aplastic anaemia, haemolytic anaemia, lymphadenopathy		Transient increase in serum IgM levels ⁴	Late Neutropenia ⁴

Immune system disorders	Infusion related reactions ⁵ , angioedema	Hypersensitivity		Anaphylaxis	Tumour lysis syndrome, cytokine release syndrome ⁵ , serum sickness	Infusion related acute reversible thrombocytopenia ⁵
Metabolism and nutrition disorders		Hyperglycaemia, weight decrease, peripheral oedema, face oedema, increased LDH, hypocalcaemia				
Psychiatric disorders			Depression, nervousness			
Nervous system disorders		Paraesthesia, hypoaesthesia, agitation, insomnia, vasodilatation, dizziness, anxiety	Dysgeusia		Peripheral neuropathy, facial nerve palsy ⁶	Cranial neuropathy, loss of other senses ⁶
Eye disorders		Lacrimation disorder, conjunctivitis			Severe vision loss ⁶	
Ear and labyrinth disorders		Tinnitus, ear pain				Hearing loss ⁶
Cardiac disorders		*Myocardial Infarction ^{5,7} , arrhythmia, *atrial fibrillation, tachycardia, *cardiac disorder	*Left ventricular failure, *supraventricular tachycardia, *ventricular tachycardia, *angina, *myocardial ischaemia, bradycardia	Severe cardiac disorders ^{5,7}	Heart failure ^{5,7}	
Vascular disorders		Hypertension, orthostatic hypotension, hypotension			Vasculitis (predominately cutaneous), leukocytoclastic vasculitis	
Respiratory, thoracic and mediastinal disorders		Bronchospasm ⁵ , Respiratory disease, chest pain, dyspnoea, Increased cough, rhinitis	Asthma, bronchiolitis obliterans, lung disorder, hypoxia	Interstitial lung disease ⁸	Respiratory failure ⁵	Lung infiltration
Gastrointestinal disorders	Nausea	Vomiting, diarrhoea, abdominal pain, dysphagia, stomatitis, constipation, dyspepsia, anorexia, throat irritation	Abdominal enlargement		Gastrointestinal perforation ⁸	
Skin and subcutaneous tissue disorders	Pruritis, rash, *alopecia	Urticaria, sweating, night sweats, *skin disorder			Severe Bullous skin reactions, Stevens-Johnson Syndrome,	

					Toxic epidermal necrolysis (Lyell's Syndrome) ^{7,8}	
Musculoskeletal and connective tissue disorders		Hypertonia, myalgia, arthralgia, back pain, neck pain, pain				
Renal and urinary disorders					Renal failure ⁵	
General disorders and administration site conditions	Fever, chills, asthenia, headache	Tumour pain, flushing, malaise, cold syndrome, *fatigue, *shivering, *multiorgan failure ⁵	Infusion site pain			
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 ($\geq$ 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 observed during post-marketing surveillance

⁴ see also section haematologic adverse reactions below

⁵ see also section infusion related reactions below. Rarely fatal cases reported

⁶ signs and symptoms of cranial neuropathy. Occurred at various times up to several months after completion of rituximab therapy

⁷ observed mainly in patients with prior cardiac condition and/or cardiotoxic chemotherapy and were mostly associated with infusion-related reactions

⁸ 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: haematotoxicity, 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, pulmonary oedema and acute reversible thrombocytopenia. Exacerbations of pre-existing cardiac conditions such as angina pectoris or congestive heart failure or severe cardiac disorders (heart failure, myocardial infarction, atrial fibrillation), pulmonary oedema, multi-organ failure, tumour lysis syndrome, cytokine release syndrome, renal failure, 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 70-80% of patients but was associated with decreased serum immunoglobulins only in a minority of patients.

Localised candida infections as well as Herpes zoster were reported at a higher incidence in the rituximab-

containing arm of randomised 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 haematopoietic 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)), enterovirus (meningoencephalitis) 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 patients 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. During the treatment course 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 $1 \times 10^9/L$ between day 24 and 42 after the last dose) or occurred with a late onset (defined as neutrophil count below $1 \times 10^9/L$ 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 thrombocytopenia was reported in 11% of patients in the R-FC group compared to 9% of patients in the FC group.

In studies of rituximab in patients with Waldenstrom's macroglobulinaemia, transient increases in serum IgM levels have been observed following treatment initiation, which may be associated with hyperviscosity and related symptoms. The transient IgM increase usually returned to at least baseline level within 4 months.

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 ischaemia) 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 disorders

During the treatment period (induction treatment phase comprising of R-CHOP for at most eight cycles), 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% R-FC, 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 recognised 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 in relapsed/refractory follicular lymphoma, 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 (≥65years)

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

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 (≥65years)

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 (GPA) and microscopic polyangiitis (MPA)

Adult induction of remission (GPA/MPA Study 1)

In GPA/MPA Study 1, 99 adult patients were treated for induction of remission of GPA and MPA with Rituximab (375 mg/m², once weekly for 4 weeks) and glucocorticoids (see section 5.1).

Tabulated list of adverse reactions

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 adult patients receiving rituximab in GPA /MPA study 1 (Rituximab n=99, at a higher frequency than the comparator group), or during postmarketing surveillance.

MedDRA System organ class Adverse reaction	Frequency
Blood and lymphatic system disorders	
Thrombocytopenia	7%
Gastrointestinal disorders	
Diarrhoea	18%
Dyspepsia	6%
Constipation	5%
General disorders and administration site conditions	
Peripheral oedema	16%
Immune system disorders	
Cytokine release syndrome	5%
Infections and infestations	
Urinary tract infection	7%
Bronchitis	5%
Herpes zoster	5%
Nasopharyngitis	5%
Serious viral infection ^{1,2}	Not known
Enteroviral meningoencephalitis ¹	Not known
Investigations	
Decreased haemoglobin	6%
Metabolism and nutrition disorders	
Hyperkalaemia	5%
Musculoskeletal and connective tissue disorders	
Muscle spasms	18%
Arthralgia	15%
Back pain	10%
Muscle weakness	5%
Musculoskeletal pain	5%
Pain in extremities	5%
Nervous system disorders	
Dizziness	10%
Tremor	10%
Psychiatric disorders	

Insomnia	14%
Respiratory, thoracic and mediastinal disorders	
Cough	12%
Dyspnoea	11%
Epistaxis	11%
Nasal congestion	6%
Skin and subcutaneous tissue disorders	
Acne	7%
Vascular disorders	
Hypertension	12%
Flushing	5%

¹Observed during post-marketing surveillance.

² See also section infections below.

Description of selected adverse drug reactions

Infusion related reactions

In GPA/MPA Study 1 (adult induction of remission study), 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.

Infections

In GPA/MPA Study 1, the overall rate of infection was approximately 237 per 100 patient years (95% CI 197 - 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%.

The most common infections in the overall phase were: upper respiratory tract infections (URTIs) (48%), influenza (24%), conjunctivitis (20%), nasopharyngitis (20%), lower respiratory tract infections (16%), sinusitis (16%), viral URTIs (16%), ear infection (12%), gastroenteritis (12%), pharyngitis (12%), urinary tract infection (12%). Serious infections were reported in 7 patients (28%), and included: influenza (2 patients [8%]) and lower respiratory tract infection (2 patients [8%]) as the most frequently reported events.

In the post marketing setting, serious viral infections have been reported in GPA/MPA patients treated with rituximab.

Malignancies

In GPA/MPA Study 1, the incidence of malignancy in rituximab treated patients in the GPA and MPA 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 standardized incidence ratios, the incidence of malignancies appears to be similar to that previously reported in patients with ANCA-associated vasculitis.

Cardiovascular adverse reactions

In GPA/MPA Study 1, cardiac events occurred at a rate of approximately 273 per 100 patient years (95% CI 149-470) at the 6-month primary endpoint. The rate of serious cardiac events was 2.1 per 100 patient years (95% CI 3-15). The most frequently reported events were tachycardia (4%) and atrial fibrillation (3%) (see section 4.4).

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 adult GPA and MPA patients treated with rituximab.

In GPA/MPA Study 1, 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. The rate of overall infections and serious infections was not increased after the development of low IgA, IgG or IgM.

Neutropenia

In GPA/MPA Study 1, 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.

Skin and subcutaneous tissue disorders

Toxic epidermal necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome, some with fatal outcome, have been reported very rarely.

4.9 Overdose

Limited experience with doses higher than the approved intravenous doses of rituximab is available from study. The highest IV dose tested to date is 5000mg (2250 mg/m²), tested in a dose escalation study in patients with chronic lymphocytic leukaemia. No additional safety signals were identified. Patients who experience overdose should have immediate interruption of their infusion and be closely monitored.

Patients who experience overdose should have immediate interruption or reduction of their infusion and be closely supervised.

Consideration should be given to the need for regular monitoring of blood cell count and for increased risk of infections while patients are B cell-depleted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

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

Rixathon is a biosimilar medicinal product.

Information below refers to MabThera

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 CD20 antigen on B lymphocytes has also been demonstrated to induce cell death via apoptosis.

Clinical efficacy and safety

Information below refers to MabThera

Peripheral B-cell counts declined below normal following completion of the first dose of rituximab. In patients treated for hematological 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).

In GPA and MPA patients, the number of peripheral blood B-cells decreased to <10 cells/μl two weekly infusions of rituximab 375mg/m², and remained at that level in most patients up to the 6 month timepoint. 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.

Clinical experience in Non-Hodgkin's lymphoma and in chronic lymphocytic leukaemia

Follicular lymphoma

Monotherapy

Initial treatment, weekly for 4 doses

In the pivotal trial, 166 patients with relapsed or chemoresistant low-grade or follicular B cell NHL received 375mg/m² of rituximab as an intravenous infusion once weekly for four weeks. The overall response rate (ORR) in the intent-to-treat (ITT) population was 48 % (CI95% 41% - 56%) with a 6% complete response (CR) and a 42 % partial response (PR) rate. The projected median time to progression (TTP) for responding patients was 13.0 months. In a subgroup analysis, the ORR was higher in patients with IWF B, C, and D histological subtypes as compared to IWF A subtype (58 % vs. 12%), higher in patients whose largest lesion was <5 cm vs. >7 cm in greatest diameter (53% vs. 38%), and higher in patients with chemosensitive relapse as compared to chemoresistant (defined as duration of response <3 months) relapse (50% vs. 22%). ORR in patients previously treated with autologous bone marrow transplant (ABMT) was 78% versus 43% in patients with no ABMT. Neither age, sex, lymphoma grade, initial diagnosis, presence or absence of bulky disease, normal or high LDH nor presence of extranodal disease had a statistically significant effect (Fisher's exact test) on response to rituximab. A statistically significant correlation was noted between response rates and bone marrow involvement. 40% of patients with bone marrow involvement responded compared to 59% of patients with no bone marrow involvement (p=0.0186). This finding was not supported by a stepwise logistic regression analysis in which the following factors were identified as prognostic factors: histological type, bcl-2 positivity at baseline, resistance to last chemotherapy and bulky disease.

Initial treatment, weekly for 8 doses

In a multi-centre, single-arm trial, 37 patients with relapsed or chemoresistant, low grade or follicular B cell NHL received 375 mg/m² of rituximab as intravenous infusion weekly for eight doses. The ORR was 57% (95% Confidence interval (CI); 41% – 73%; CR 14%, PR 43%) with a projected median TTP for responding patients of 19.4 months (range 5.3 to 38.9 months).

Initial treatment, bulky disease, weekly for 4-doses

In pooled data from three trials, 39 patients with relapsed or chemoresistant, bulky disease (single lesion ≥10 cm in diameter), low grade or follicular B cell NHL received 375 mg/m² of rituximab as intravenous infusion weekly for four doses. The ORR was 36 % (CI95% 21% – 51%; CR 3%, PR 33%) with a median TTP for responding patients of 9.6 months (range 4.5 to 26.8 months).

Re-treatment, weekly for 4 doses

In a multi-centre, single-arm trial, 58 patients with relapsed or chemoresistant low grade or follicular B cell NHL, who had achieved an objective clinical response to a prior course of rituximab, were re-treated with

375 mg/m² of rituximab as intravenous infusion weekly for four doses. Three of the patients had received two courses of rituximab before enrolment and thus were given a third course in the study. Two patients were re-treated twice in the study. For the 60 re-treatments on study, the ORR was 38% (CI95% 26% – 51%; 10% CR, 28% PR) with a projected median TTP for responding patients of 17.8 months (range 5.4 – 26.6). This compares favourably with the TTP achieved after the prior course of rituximab (12.4 months).

Initial treatment, in combination with chemotherapy

In an open-label randomised trial, a total of 322 previously untreated patients with follicular lymphoma were randomised to receive either CVP chemotherapy (cyclophosphamide 750 mg/m², vincristine 1.4 mg/m² up to a maximum of 2 mg on day 1, and prednisolone 40 mg/m²/day on days 1 - 5) every 3 weeks for 8 cycles or rituximab 375 mg/m² in combination with CVP (R-CVP). Rituximab was administered on the first day of each treatment cycle. A total of 321 patients (162 R-CVP, 159 CVP) received therapy and were analysed for efficacy. The median follow-up of patients was 53 months. R-CVP led to a significant benefit over CVP for the primary endpoint, time to treatment failure (27 months vs. 6.6 months, $p < 0.0001$, log-rank test). The proportion of patients with a tumour response (CR, CRu, PR) was significantly higher ($p < 0.0001$ Chi-Square test) in the R-CVP group (80.9%) than the CVP group (57.2%). Treatment with R-CVP significantly prolonged the time to disease progression or death compared to CVP, 33.6 months and 14.7 months, respectively ($p < 0.0001$, log-rank test). The median duration of response was 37.7 months in the R-CVP group and was 13.5 months in the CVP group ($p < 0.0001$, log-rank test).

The difference between the treatment groups with respect to overall survival showed a significant clinical difference ($p=0.029$, log-rank test stratified by centre): survival rates at 53 months were 80.9% for patients in the R-CVP group compared to 71.1% for patients in the CVP group.

Results from three other randomised trials using rituximab in combination with chemotherapy regimen other than CVP (CHOP, MCP, CHVP/Interferon- α) have also demonstrated significant improvements in response rates, time-dependent parameters as well as in overall survival.

Maintenance therapy

Previously untreated follicular lymphoma

In a prospective, open label, international, multi-centre, phase III trial 1193 patients with previously untreated advanced follicular lymphoma received induction therapy with R-CHOP ($n=881$), R-CVP ($n=268$) or R-FCM ($n=44$), according to the investigators' choice. A total of 1078 patients responded to induction therapy, of which 1018 were randomised to rituximab maintenance therapy ($n=505$) or observation ($n=513$). The two treatment groups were well balanced with regards to baseline characteristics and disease status. Rituximab maintenance treatment consisted of a single infusion of rituximab at 375 mg/m² body surface area given every 2 months until disease progression or for a maximum period of two years.

The pre-specified primary analysis was conducted at a median observation time of 25 months from randomization, maintenance therapy with rituximab resulted in a clinically relevant and statistically significant improvement in the primary endpoint of investigator assessed progression-free survival (PFS) as compared to observation in patients with previously untreated follicular lymphoma.

Significant benefit from maintenance treatment with rituximab was also seen for the secondary endpoints event-free survival (EFS), time to next anti-lymphoma treatment (TNLT) time to next chemotherapy (TNCT) and overall response rate (ORR) in the primary analysis.

Data from extended follow-up of patients in the study (median follow-up 9 years) confirmed the long-term benefit of rituximab maintenance therapy in terms of PFS, EFS, TNLT and TNCT.

Rituximab maintenance treatment provided consistent benefit in all predefined subgroups tested: gender (male, female), age (<60 years, ≥ 60 years), FLIPI score (≤ 1 , 2 or ≥ 3), induction therapy (R-CHOP, R-CVP or R-FCM) and regardless of the quality of response to induction treatment (CR, CRu or PR). Exploratory analyses of the benefit of maintenance treatment showed a less pronounced effect in elderly patients (>70 years of age), however sample sizes were small.

Relapsed/Refractory follicular lymphoma

In a prospective, open label, international, multi-centre, phase III trial, 465 patients with relapsed/refractory follicular lymphoma were randomised in a first step to induction therapy with either CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone; n=231) or rituximab plus CHOP (R-CHOP, n=234). The two treatment groups were well balanced with regard to baseline characteristics and disease status. A total of 334 patients achieving a complete or partial remission following induction therapy were randomised in a second step to rituximab maintenance therapy (n=167) or observation (n=167). Rituximab maintenance treatment consisted of a single infusion of rituximab at 375 mg/m² body surface area given every 3 months until disease progression or for a maximum period of two years.

The final efficacy analysis included all patients randomised to both parts of the study. After a median observation time of 31 months for patients randomised to the induction phase, R-CHOP significantly improved the outcome of patients with relapsed/refractory follicular lymphoma when compared to CHOP.

For patients randomised to the maintenance phase of the trial, the median observation time was 28 months from maintenance randomisation. Maintenance treatment with rituximab led to a clinically relevant and statistically significant improvement in the primary endpoint, PFS, (time from maintenance randomisation to relapse, disease progression or death) when compared to observation alone (p< 0.0001 log-rank test). The median PFS was 42.2 months in the rituximab maintenance arm compared to 14.3 months in the observation arm. Using a cox regression analysis, the risk of experiencing progressive disease or death was reduced by 61% with rituximab maintenance treatment when compared to observation (95% CI; 45%-72%). Kaplan-Meier estimated progression-free rates at 12 months were 78% in the rituximab maintenance group vs. 57 % in the observation group. An analysis of overall survival confirmed the significant benefit of rituximab maintenance over observation (p=0.0039 log-rank test). Rituximab maintenance treatment reduced the risk of death by 56% (95% CI; 22%-75%).

The benefit of rituximab maintenance treatment was confirmed in all subgroups analysed, regardless of induction regimen (CHOP or R-CHOP) or quality of response to induction treatment (CR or PR) (Table 7). Rituximab maintenance treatment significantly prolonged median PFS in patients responding to CHOP induction therapy (median PFS 37.5 months vs. 11.6 months, p< 0.0001) as well as in those responding to R-CHOP induction (median PFS 51.9 months vs. 22.1 months, p=0.0071). Although subgroups were small, rituximab maintenance treatment provided a significant benefit in terms of overall survival for both patients responding to CHOP and patients responding to R-CHOP, although longer follow-up is required to confirm this observation.

Adult Diffuse large B cell non-Hodgkin's lymphoma

In a randomised, open-label trial, a total of 399 previously untreated elderly patients (age 60 to 80 years) with diffuse large B cell lymphoma received standard CHOP chemotherapy (cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², vincristine 1.4 mg/m² up to a maximum of 2 mg on day 1, and prednisolone 40 mg/m²/day on days 1-5) every 3 weeks for eight cycles, or rituximab 375 mg/m² plus CHOP (R-CHOP). Rituximab was administered on the first day of the treatment cycle.

The final efficacy analysis included all randomised patients (197 CHOP, 202 R-CHOP), and had a median follow-up duration of approximately 31 months. The two treatment groups were well balanced in baseline disease characteristics and disease status. The final analysis confirmed that R-CHOP treatment was associated with a clinically relevant and statistically significant improvement in the duration of event-free survival (the primary efficacy parameter; where events were death, relapse or progression of lymphoma, or institution of a new anti-lymphoma treatment) (p=0.0001). Kaplan Meier estimates of the median duration of event-free survival were 35 months in the R-CHOP arm compared to 13 months in the CHOP arm, representing a risk reduction of 41%. At 24 months, estimates for overall survival were 68.2% in the R-CHOP arm compared to 57.4% in the CHOP arm. A subsequent analysis of the duration of overall survival, carried out with a median follow-up duration of 60 months, confirmed the benefit of R-CHOP over CHOP treatment (p=0.0071), representing a risk reduction of 32%.

The analysis of all secondary parameters (response rates, progression-free survival, disease-free survival, duration of response) verified the treatment effect of R-CHOP compared to CHOP. The complete response

rate after cycle 8 was 76.2% in the R-CHOP group and 62.4% in the CHOP group ($p=0.0028$). The risk of disease progression was reduced by 46% and the risk of relapse by 51%.

In all patient subgroups (gender, age, age adjusted IPI, Ann Arbor stage, ECOG, $\beta 2$ microglobulin, LDH, albumin, B symptoms, bulky disease, extranodal sites, bone marrow involvement), the risk ratios for event-free survival and overall survival (R-CHOP compared with CHOP) were less than 0.83 and 0.95 respectively. R-CHOP was associated with improvements in outcome for both high- and low risk patients according to age adjusted IPI.

Clinical laboratory findings

Of 67 patients evaluated for human anti-mouse antibody (HAMA), no responses were noted. Of 356 patients evaluated for anti-drug antibody (ADA), 1.1% (4 patients) were positive.

Chronic lymphocytic leukaemia

In two open-label randomised trials, a total of 817 previously untreated patients and 552 patients with relapsed/refractory CLL were randomised to receive either FC chemotherapy (fludarabine 25 mg/m², cyclophosphamide 250 mg/m², days 1-3) every 4 weeks for 6 cycles or rituximab in combination with FC (RFC). Rituximab was administered at a dosage of 375 mg/m² during the first cycle one day prior to chemotherapy and at a dosage of 500 mg/m² on day 1 of each subsequent treatment cycle. Patients were excluded from the study in relapsed/refractory CLL if they had previously been treated with monoclonal antibodies or if they were refractory (defined as failure to achieve a partial remission for at least 6 months) to fludarabine or any nucleoside analogue. A total of 810 patients (403 R-FC, 407 FC) for the first-line study and 552 patients (276 R-FC, 276 FC) for the relapsed/refractory study were analysed for efficacy. In the first-line study, after a median observation time of 48.1 months, the median PFS was 55 months in the RFC group and 33 months in the FC group ($p < 0.0001$, log-rank test). The analysis of overall survival showed a significant benefit of R-FC treatment over FC chemotherapy alone ($p = 0.0319$, log-rank test). The benefit in terms of PFS was consistently observed in most patient subgroups analysed according to disease risk at baseline (i.e. Binet stages A-C).

In the relapsed/refractory study, the median progression-free survival (primary endpoint) was 30.6 months in the R-FC group and 20.6 months in the FC group ($p=0.0002$, log-rank test). The benefit in terms of PFS was observed in almost all patient subgroups analysed according to disease risk at baseline. A slight but not significant improvement in overall survival was reported in the R-FC compared to the FC arm.

Results from other supportive studies using rituximab in combination with other chemotherapy regimens (including CHOP, FCM, PC, PCM, bendamustine and cladribine) for the treatment of previously untreated and/or relapsed/refractory CLL patients have also demonstrated high overall response rates with benefit in terms of PFS rates, albeit with modestly higher toxicity (especially myelotoxicity). These studies support the use of rituximab with any chemotherapy.

Data in approximately 180 patients pre-treated with rituximab have demonstrated clinical benefit (including CR) and are supportive for rituximab re-treatment.

Clinical experience in granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA)

Adult induction of remission

In GPA/MPA Study 1, a total of 197 patients aged 15 years or older with severe active GPA (75%) and MPA (24%) were enrolled and treated in an active-comparator, randomised, double-blind, multicenter, non-inferiority trial.

Patients were randomised in a 1:1 ratio to receive either oral cyclophosphamide daily (2 mg/kg/day) for 3-6 months or rituximab (375 mg/m²) once weekly for 4 weeks. All patients in the cyclophosphamide arm received azathioprine maintenance therapy in during follow-up. Patients in both arms received 1000 mg of pulse intravenous (IV) methylprednisolone (or another equivalent-dose glucocorticoid) per day for 1 to 3 days, followed by oral prednisone (1 mg/kg/day, not exceeding 80 mg/day). Prednisone tapering was to be completed by 6 months from the start of trial treatment.

The primary outcome measure was achievement of complete remission at 6 months defined as a

Birmingham Vasculitis Activity Score for Wegener's granulomatosis (BVAS/WG) of 0, and off glucocorticoid therapy. The prespecified non-inferiority margin for the treatment difference was 20%. The trial demonstrated noninferiority of rituximab to cyclophosphamide for complete remission (CR) at 6 months.

Complete remission at 12 and 18 months

In the rituximab group, 48% of patients achieved CR at 12 months, and 39% of patients achieved CR at 18 months. In patients treated with cyclophosphamide (followed by azathioprine for maintenance of complete remission), 39% of patients achieved CR at 12 months, and 33% of patients achieved CR at 18 months. From month 12 to month 18, 8 relapses were observed in the rituximab group compared with four in the cyclophosphamide group.

Laboratory evaluations

A total of 23/99 (23%) rituximab-treated patients from the induction of remission trial tested positive for ADA by 18 months. None of the 99 rituximab-treated patients were ADA positive at screening. There was no apparent trend or negative impact of the presence of ADA on safety or efficacy in the induction of remission trial.

Comparability of Rixathon to MabThera

Information below refers to biosimilar Rixathon

Clinical studies conducted to support similarity between Rixathon and the reference biologic drug included:

- A comparative pharmacokinetic (PK) / pharmacodynamic (PD), safety, efficacy and immunogenicity study in patients with rheumatoid arthritis (RA) refractory or intolerant to standard DMARDs and one or up to three anti-TNF therapies (GP13-201 (GPN013A2301)).
- A comparative efficacy, safety and pharmacokinetics study of Rixathon plus CVP vs. MabThera (EU-authorized rituximab) plus CVP in patients with untreated, advanced stage Follicular Lymphoma (GP13-301 (IGG013A2301J)).

An overview of the study design(s) and demographic characteristics of patients enrolled in each clinical study is presented in table below.

Table 4: Summary of trial designs and patient demographics

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
GP13-201 (GPN013A2301) Rheumatoid Arthritis	Phase II, Double Blind; Parallel Group; Randomized; Multicentre	Rixathon, 1000 mg iv - on two separate occasions, 2 weeks apart MabThera, 1000 mg iv - on two separate occasions, 2 weeks apart Rituxan, 1000 mg iv - on two separate occasions, 2 weeks apart Treatment period - 52 weeks, plus 26-week	Total randomized: N=312 (Part I N=173, Part II N=139) Rixathon (Part I N=86, Part II N=47; Total: N=133) MabThera (Part I): N=87 Rituxan (Part II): N=92	Part I: 53.7 years (range: 21-82) Rixathon: 54.7 (range 26-82) MabThera: 52.7 (range 21-79) Part II: 54.6 years (range: 26 to 82 years) Rixathon: 54.4 (range 26-82) Rituxan: 55.0 (range :30-78)	Part I: Males: 24 (13.9%); Females: 149 (86.1%) Rixathon: Males: 10 (11.6%); Females:76 (88.4%) MabThera: Males: 14 (16.1%); Females: 73 (83.9%) Part II: Males 36 (16.0%); Females 189 (84.0%) Rixathon: Males: 22

		retreatment follow-up period after first infusion of the second course of study medication			(16.5%); Females: 111 (83.5%) Rituxan: Males: 14 (15.2%); Females 78 (84.8%)
GP13-301 (IGG013A2301J) / Follicular Lymphoma	Phase III, Parallel Group; Randomized Stratified; Active Comparator Controlled	Combination Treatment Period: Total 8 cycles of Rixathon or MabThera 375 mg/m ² (10 mg/L in 500 mg (50 mL) single use vials), i.v. on Day 1 of each cycle + CVP administered every 21 days (±3 days)	Total randomized: N=627 (treated) + 2 (untreated) = 629 GP2013: N=312 MabThera: N=315	56.9 years (range: 23-84 years) Rixathon: 57.5 years (range: 23- 84) MabThera: 56.4 years (range: 24- 84)	Males: 277 (44.2%); Females: 350 (55.8%) Rixathon: Males: 131 (42.0%); Females: 181 (58.0%) MabThera: Males: 146 (46.3%); Females: 169 (53.7%)

MabThera = EU-authorized rituximab

Rituxan = US-authorized rituximab

Comparative Study Results

Comparative Bioavailability Studies

Pharmacokinetics (PK) results from study GP13-201 (GPN013A2301) – Rheumatoid Arthritis

The pharmacokinetics of Rixathon were compared to MabThera in Part I of a randomized, double-blind clinical study in adult patients with rheumatoid arthritis refractory or intolerant to standard DMARDs and one or up to three anti-TNF therapies. The bioequivalence criteria were met for the PK parameters AUCT and C_{MAX,1} (C_{MAX} after the first infusion). The point estimate and 90%CI of the Geometric mean ratio (GMR) of AUCT from Rixathon/MabThera were within the acceptance margins of 0.80 to 1.25 (see below table). The GMR for C_{MAX,1} was 1.133, which falls within the acceptance margins of 0.80 to 1.25.

Table 5: Part I of Study GP13-201: Analysis of Primary Pharmacokinetic Parameters

Rituximab 1000 mg, 2 single doses (from measured data)				
Adjusted Geometric Means				
Parameter	Rixathon¹	MabThera²	Ratio (Test/Reference) of Geometric Means (%)	90% Confidence Interval (%)
AUCT (ug/mL*day)	6696.36	6159.42	108.7	98.0-120.6
AUCI (ug/mL*day)	6738.51	6334.41	106.4	96.8-116.9
C _{MAX,1} (ug/mL)	341.67	301.62	113.3	101.7-126.2

T _{1/2} ³ (h)	380.07 (41.58%)	379.40 (27.82%)		
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[1] Rixathon (rituximab), Sandoz.

[2] MabThera (rituximab), Hoffman LaRoche Inc., source: European Union

[3] T_{1/2} expressed as the arithmetic mean (CV%)

Abbreviations: AUC_T – Area under the concentration time curve from time zero to the last measureable concentration; AUC_I – Area under the concentration time curve from time zero to infinity; C_{max,1} – maximum observed concentration after the first rituximab administration; T_{1/2} – elimination half-life.

Comparative Safety and Efficacy

Efficacy

Study GP13-301 (IGG013A2301J) - Non-Hodgkin's Lymphoma

The efficacy and safety of Rixathon was compared to MabThera in a randomized, double-blind clinical study in adult patients with untreated, Stage III/ IV, CD20-positive follicular lymphoma (FL). Eligible patients were randomized in a 1:1 ratio to receive 8 cycles of either Rixathon in combination with CVP or MabThera in combination with CVP. The study was designed to rule out any clinically meaningful differences between Rixathon and MabThera. The primary variable was Objective Response Rate (ORR) during the combination phase, assessed using the Modified Response Criteria for Malignant Lymphoma through central blinded review of the radiological response. Comparability between Rixathon and MabThera was demonstrated since the two-sided 95% confidence interval of the risk difference in ORR after 8 cycles of combination treatment was entirely contained within the pre-defined equivalence interval of [-12% to 12%] (Table 6).

Table 6: Study GP13-301 (IGG013A2301J): Primary efficacy analysis of ORR based on the Modified Response Criteria for Malignant Lymphoma (FAS) after the combination treatment phase

	Rixathon N=312	MabThera N=315	Rixathon– MabThera	
	n (%)	n (%)	Diff %	[95% CI] ¹
Overall response rate (CR or PR)	272(87.2)	276 (87.6)	-0.44	[-5.95, 5.07]

CI=Confidence interval; CR=Complete response; FAS=Full Analysis Set; ORR=Overall response rate; PR=Partial response

¹The 95% CI for the difference in proportions is based on normal approximation to the binomial distribution.

Safety

The types, frequency and severity of adverse events were comparable between Rixathon and the reference biologic drug; please refer to Part I Adverse Reactions section.

Immunogenicity

Immunogenicity of Rixathon was assessed for rheumatoid arthritis and follicular lymphoma patients in studies GP13-201 (GPN013A2301) and GP13-301 (IGG013A2301J), respectively. Sensitive immunoassays for the detection of ADAs and cell based assays to characterize the neutralizing capacity were developed and fully validated. Dedicated assay formats were optimized for each indication and applied in corresponding studies while the sensitivity of the ADA assay applied in study GP13-201 (GPN013A2301) was higher compared to the assay used in GP13-301 (IGG013A2301J). Immunogenicity evaluation followed a tiered approach comprising a screening and confirmatory step as well as titer and neutralizing antibody assessment.

In the rheumatoid arthritis study GP13-201 (GPN013A2301), 22.2% of patients were confirmed positive for binding ADAs in Rixathon treated patients while 13.9% and 32.1% of Rituxan and MabThera treated patients developed anti-drug antibodies, respectively.

In the follicular lymphoma study GP13-301 (IGG013A2301J), immunogenicity was detected in 1.8% of patients in Rixathon group and 1.1% in MabThera group.

Overall, the immunogenicity profile of Rixathon was similar to Rituxan and MabThera. While the majority of patients in both studies did not develop ADAs, the detected ADA responses were mainly transient of low titer and non-neutralizing.

Of note, immunogenicity assay results are highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications and underlying disease.

5.2 Pharmacokinetic properties

5.2.1 Distribution

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, the typical population estimates of nonspecific clearance (CL_1), specific clearance (CL_2) likely contributed by B cells or tumor 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 tumor lesions contributed to some of the variability in CL_2 of rituximab in data from 161 patients given 375 mg/m² as an i.v. infusion for 4 weekly doses. Patients with higher CD19-positive cell counts or tumor 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 tumor 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 m²) and concurrent CHOP therapy, respectively, were relatively small. Age, gender, race, 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 at a dose of 375 mg/m² was administered as an i.v. infusion at weekly intervals for 4 doses to 203 patients with NHL naive to rituximab. The mean C_{max} following the fourth infusion was 486 µg/mL (range, 77.5 to 996.6 µg/mL). The peak and trough serum levels of rituximab were inversely correlated with baseline values for the number of circulating CD19-positive B-cells and measures of disease burden. Median steady-state serum levels were higher for responders compared with non-responders. Serum levels were higher in patients with International Working Formulation (IWF) subtypes B, C, and D as compared with those with subtype A. Rituximab was detectable in the serum of patients 3 – 6 months after completion of last treatment.

Rituximab at a dose of 375 mg/m² was administered as an i.v. 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/m² in combination with 6 cycles of CHOP chemotherapy was similar to that seen with rituximab alone.

Chronic Lymphocytic Leukemia

Rituximab was administered as an i.v. infusion at a first-cycle dose of 375 mg/m² increased to 500 mg/m² 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/m² infusion.

Granulomatosis with Polyangiitis (Wegener's) (GPA) and Microscopic Polyangiitis (MPA)

Based on the population pharmacokinetic analysis of data in 97 GPA and MPA patients who received 375 mg/m² rituximab once weekly for four 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, 0.116 to 0.726 L/day) and 4.50 L (range, 2.25 to 7.39 L), respectively.

5.2.2 Elimination

See 5.2.1 Distribution.

5.2.3 Pharmacokinetics in Special Populations

No pharmacokinetic data are available in patients with hepatic or renal impairment.

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 postnatally 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

Sodium citrate
Polysorbate 80
Sodium chloride
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)
Water for injections

6.2 Incompatibilities

No incompatibilities between Rixathon and polyvinyl chloride or polyethylene bags or infusion sets have been observed.

6.3 Shelf life

Unopened vial

3 years at 2°C – 8°C.

Rixathon may be stored at temperatures up to a maximum of 30°C for a single period of up to 7 days, but not exceeding the original expiry date. The new expiry date must be written on the carton. Upon removal from refrigerated storage, Rixathon must not be returned to refrigerated storage.

Diluted solution

- After aseptic dilution in sodium chloride solution:

Chemical and physical stability of Rixathon diluted in 0.9% sodium chloride solution has been demonstrated for 30 days at 2°C - 8°C and 7 days $\leq$ 30°C, protected from light.

- After aseptic dilution in glucose solution:

Chemical and physical stability of Rixathon diluted in 5% glucose solution has been demonstrated for 24 hours at 2°C - 8°C and subsequently 12 hours at room temperature ($\leq$ 25°C).

From a microbiological point of view, the prepared infusion solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

Keep the container in the outer carton in order to protect from light.

For storage conditions of the unopened vial outside the refrigerator, see section 6.3.

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

6.5 Nature and contents of container

10 mL vial: Clear Type I glass vials with butyl rubber stopper containing 100 mg of rituximab in 10 mL. Packs of 2 or 3 vials.

50 mL vial: Clear Type I glass vials with butyl rubber stopper containing 500 mg of rituximab in 50 mL. Packs of 1 or 2 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Rixathon is provided in sterile, preservative-free, non-pyrogenic, single use vials.

Aseptic preparation

Aseptic handling must be ensured when preparing the infusion. Preparation should be:

- performed under aseptic conditions by trained personnel in accordance with good practice rules especially with respect to the aseptic preparation of parenteral products.
- prepared in a laminar flow hood or biological safety cabinet using standard precautions for the safe handling of intravenous agents.

Aseptically withdraw the necessary amount of Rixathon, and dilute to a calculated concentration of 1 to 4 mg/mL rituximab into an infusion bag containing sterile, pyrogen-free sodium chloride 9 mg/mL (0.9%) solution for injection or 5% D-Glucose in water. For mixing the solution, gently invert the bag in order to avoid foaming. Care must be taken to ensure the sterility of prepared solutions. Since the medicinal product does not contain any anti-microbial preservative or bacteriostatic agents, aseptic technique must be observed. Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration.

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

7. PRODUCT REGISTRATION HOLDER

Sandoz Products Malaysia Sdn. Bhd.
Unit 1202, Level 12, Uptown 1,
No. 1, Jalan SS 21/58, Damansara Uptown,
47400 Petaling Jaya, Selangor, Malaysia.

Note: "Rituximab" refers to Mabthera, while "biosimilar" refers to Rixathon.

8. DATE OF REVISION

August 2025