NEW ZEALAND DATA SHEET

RIXIMYO®
Rituximab (rch)
100 mg in 10 mL and 500 mg in 50 mL concentrate for solution for intravenous (IV) infusion

1. PRODUCT NAME

RIXIMYO® rituximab (rch) concentrate for solution for intravenous infusion 100mg/10mL & 500mg/50mL vial.

RIXIMYO® is a biosimilar medicine.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL concentrate for solution for infusion contains 10 mg rituximab.

Description

Rituximab is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. The antibody is a glycosylated IgG1 kappa immunoglobulin containing murine light- and heavy-chain variable region sequences (Fab domain) and human constant region sequences (Fc domain). Rituximab has a high binding affinity for the CD20 antigen of 5.2 to 11.0 nM. Rituximab has a molecular mass of 145 kDa and is composed of two light chains (213 amino acids) and two N-glycosylated heavy chains (451 amino acid), which are covalently associated with one another at defined cysteine residues via disulfide bridges.

The chimeric anti-CD20 antibody is produced by recombinant DNA technology in a mammalian (Chinese hamster ovary) cell expression system. The anti-CD20 antibody is purified by affinity chromatography and ion exchange, including specific viral inactivation and removal procedures.

For the full list of excipients, see section 6.1.

RIXIMYO® is a biosimilar medicine to the reference medicine Mabthera®. The prescribing physician should be involved in any decision regarding interchangeability with other products. Additional information is available on the following website (www.medsafe.govt.nz/profs/RIss/Biosimilars.asp).

In studies comparing the pharmaceutical quality and the biological activity, as well as in nonclinical and clinical comparative studies it was demonstrated that RIXIMYO® matches the reference medicine in terms of quality, safety, efficacy and immunogenicity. The level of comparability of RIXIMYO® with the reference medicine that has been shown justifies the use of RIXIMYO® in all indications of the reference medicine. Data comparing RIXIMYO® to the reference medicine can be found in Section 5.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for intravenous infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rituximab is indicated in adults for the following indications:

Non-Hodgkin's lymphoma (NHL)

RIXIMYO® is indicated for the treatment of patients with:

- CD20 positive, previously untreated low-grade or follicular, B-cell non-Hodgkin's lymphoma incombination with chemotherapy,
- CD20 positive, relapsed or chemoresistent low-grade or follicular, B-cell non-Hodgkin's lymphoma,
- CD20 positive, diffuse large B-cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) chemotherapy.

RIXIMYO® is indicated for the maintenance treatment of patients with CD20 positive, low grade or follicular, B-cell non-Hodgkin's lymphoma.

Chronic lymphocytic leukaemia (CLL)

RIXIMYO® in combination with chemotherapy is indicated for the treatment of patients with chronic lymphocytic leukaemia (CLL).

Rheumatoid arthritis

RIXIMYO® in combination with methotrexate is indicated for the treatment of patients with severe active rheumatoid arthritis who have had an inadequate response or intolerance to other disease modifying agents.

Granulomatosis with polyangiitis and microscopic polyangiitis

RIXIMYO® in combination with glucocorticoids is indicated for the induction of remission in patients with severely active Granulomatosis with polyangiitis (GPA, also known as Wegener's granulomatosis) and Microscopic polyangiitis (MPA).

4.2 Dose and method of administration

RIXIMYO® should be administered under the close supervision of an experienced healthcare professional, and in an environment where full resuscitation facilities are immediately available (see section 4.4).

Premedication consisting of an anti-pyretic and an antihistaminic, e.g. paracetamol and diphenhydramine, should always be given before each administration of RIXIMYO®.

In patients with non-Hodgkin's lymphoma and chronic lymphocytic leukaemia, premedication with glucocorticoids should be considered if RIXIMYO® is not given in combination with glucocorticoid-containing chemotherapy. In patients with rheumatoid arthritis, premedication with 100 mg intravenous methylprednisolone should be completed 30 minutes prior to RIXIMYO® infusions to decrease the incidence and severity of infusion related reactions (IRRs).

In patients with granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis, methylprednisolone given intravenously for 1 to 3 days at a dose of 1,000 mg per day is recommended prior to the first infusion of RIXIMYO® (the last dose of methylprednisolone may be given on the same day as the first infusion of RIXIMYO®). 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 rituximab treatment.

Posology

It is important to check the medicinal product labels to ensure that the appropriate formulation is being given to the patient, as prescribed.

Non-Hodgkin's lymphoma (NHL)

Follicular non-Hodgkin's lymphoma

Combination therapy

The recommended dose of RIXIMYO® in combination with chemotherapy for induction treatment of previously untreated or relapsed/ refractory patients with follicular lymphoma is: 375 mg/m^2 body surface area per cycle, for up to 8 cycles.

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

Maintenance therapy

- Previously untreated follicular lymphoma

The recommended dose of RIXIMYO® used as a maintenance treatment for patients with previously untreated follicular lymphoma who have responded to induction treatment is: 375 mg/m^2 body surface area once every 2 months (starting 2 months after the last dose of induction therapy) until disease progression or for a maximum period of two years.

- Relapsed/refractory follicular lymphoma

The recommended dose of RIXIMYO® used as a maintenance treatment for patients with relapsed/refractory follicular lymphoma who have responded to induction treatment is: 375 mg/m^2 body surface area once every 3 months (starting 3 months after the last dose of induction therapy) until disease progression or for a maximum period of two years.

Monotherapy

- Relapsed/refractory follicular lymphoma

The recommended dose of RIXIMYO® monotherapy used as induction treatment for adult patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy is: 375 mg/m^2 body surface area, administered as an intravenous infusion once weekly for four weeks.

For retreatment with RIXIMYO® monotherapy for patients who have responded to previous treatment with rituximab monotherapy for relapsed/refractory follicular lymphoma, the recommended dose is: 375 mg/m^2 body surface area, administered as an intravenous infusion once weekly for four weeks (see section 5.1).

Diffuse large B cell non-Hodgkin's lymphoma

RIXIMYO® should be used in combination with CHOP chemotherapy. The recommended dose is 375 mg/m^2 body surface area, administered on day 1 of each chemotherapy cycle for 8 cycles after intravenous infusion of the glucocorticoid component of CHOP. Safety and efficacy of RIXIMYO® have not been established in combination with other chemotherapies in diffuse large B cell non- Hodgkin's lymphoma.

Dose adjustments during treatment

No dose reductions of RIXIMYO® are recommended. When RIXIMYO® is given in combination with chemotherapy, standard dose reductions for the chemotherapeutic medicinal products should be applied.

Chronic lymphocytic leukaemia (CLL)

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

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

Adult patients – NHL and CLL only - Alternative Subsequent, Faster Infusion Schedule:

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.

Rheumatoid arthritis (RA)

Patients treated with RIXIMYO® must be given the patient alert card with each infusion.

A course of RIXIMYO® consists of two 1,000 mg intravenous infusions. The recommended dose of RIXIMYO® is 1,000 mg by intravenous infusion followed by a second 1,000 mg intravenous infusion two weeks later.

The need for further courses should be evaluated 24 weeks following the previous course. Retreatment should be given at that time if residual disease activity remains, otherwise retreatment should be delayed until disease activity returns.

Available data suggest that clinical response is usually achieved within 16 to 24 weeks of an initial treatment course. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within this time period.

Granulomatosis with polyangiitis and microscopic polyangiitis

Patients treated with RIXIMYO® must be given the patient alert card with each infusion.

The recommended dose of RIXIMYO® for induction of remission therapy of granulomatosis with polyangiitis and microscopic polyangiitis is 375 mg/m^2 body surface area, administered as an intravenous infusion once weekly for 4 weeks (four infusions in total).

Pneumocystis jiroveci pneumonia (PCP) prophylaxis is recommended for patients with granulomatosis with polyangiitis or microscopic polyangiitis during and following RIXIMYO® treatment, as appropriate.

Special populations

Elderly population

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

Paediatric population

The safety and efficacy of rituximab in children below 18 years have not been established. No data are available.

Method of administration

RIXIMYO® is for intravenous use. The prepared RIXIMYO® solution should be administered as an intravenous infusion through a dedicated line. It should not be administered as an intravenous push or bolus.

Patients should be closely monitored for the onset of cytokine release syndrome (see Section 4.4). Patients who develop evidence of severe reactions, especially severe dyspnoea, bronchospasm or hypoxia should have the infusion interrupted immediately. Patients with non-Hodgkin's lymphoma should then be evaluated for evidence of tumour lysis syndrome including appropriate laboratory tests and, for pulmonary infiltration, with a chest X-ray. In all patients, the infusion should not be restarted until complete resolution of all symptoms, and normalisation of laboratory values and chest X-ray findings. At this time, the infusion can be initially resumed at not more than one-half the previous rate. If the same severe adverse reactions occur for a second time, the decision to stop the treatment should be seriously considered on a case by case basis.

Mild or moderate infusion-related reactions (IRR) (see Section 4.8) usually respond to a reduction in the rate of infusion. The infusion rate may be increased upon improvement of symptoms.

First infusion

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

Subsequent infusions

All indications

Subsequent doses of RIXIMYO® can be infused at an initial rate of 100 mg/h, and increased by 100 mg/h increments at 30 minute intervals, to a maximum of 400 mg/h.

Rheumatoid arthritis only

Alternative subsequent, faster, infusion schedule

If patients did not experience a serious infusion related reaction with their first or subsequent infusions of a dose of 1,000 mg RIXIMYO® administered over the standard infusion schedule, a more rapid infusion can be administered for second and subsequent infusions using the same concentration as in previous infusions (4 mg/mL in a 250 mL volume). Initiate at a rate of 250 mg/hour for the first 30 minutes and then 600 mg/hour for the next 90 minutes. If the more rapid infusion is tolerated, this infusion schedule can be used when administering subsequent infusions.

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.

4.3 Contraindications

Contraindications 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 rheumatoid arthritis, granulomatosis with polyangiitis and microscopic polyangiitis

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

Active, severe infections (see Section 4.4).

Patients in a severely immunocompromised state.

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

4.4 Special warnings and precautions for use

Traceability

In order to improve traceability of biological medicines, the tradename and batch number of the administered product should be clearly recorded in the patient medical record and/or dispensing record.

Progressive multifocal leukoencephalopathy (PML)

Use of rituximab may be associated with an increased risk of progressive multifocal leukoencephalopathy (PML). Patients must be monitored for any new or worsening neurological symptoms or signs suggestive of PML. Physicians treating patients should consider PML in the differential diagnosis of patients reporting neurological symptoms and consultation with a neurologist should be considered as clinically indicated.

Physicians should be particularly alert to symptoms suggestive of PML that the patient may not notice (e.g. cognitive, neurological or psychiatric symptoms). If such symptoms occur, further administration of rituximab should be immediately suspended until a diagnosis of PML has been excluded. To establish or exclude a diagnosis of PML evaluation including MRI scan, CSF testing for JC viral DNA and repeat neurological assessments, should be considered. Once PML has been excluded, the administration of rituximab may resume.

If a diagnosis of PML is confirmed, rituximab must be permanently discontinued. 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.

Non-Hodgkin's lymphoma and chronic lymphocytic leukaemia

Infusion related reactions

Rituximab is associated with infusion-related reactions, which may be related to release of cytokines and/or other chemical mediators. Cytokine release syndrome may be indistinguishable from acute hypersensitivity reactions. Severe infusion-related reactions with fatal outcome have been reported during post-marketing use. Severe reactions usually manifested within 30 minutes to 2 hours after

starting the first rituximab infusion, were characterised by pulmonary events and included, in some cases, rapid tumour lysis and features of tumour lysis syndrome in addition to fever, chills, rigors, hypotension, urticaria, angio-oedema and other symptoms. Patients with a high tumour burden or with a high number (> 25 x 10^9/L) of circulating malignant cells such as patients with chronic lymphocytic leukaemia (CLL) and mantle cell lymphoma may be at higher risk of developing severe infusion-related reactions. Infusion reaction symptoms are usually reversible with interruption of the infusion. Treatment of infusion-related symptoms with an antihistamine and an analgesic/antipyretic (such as paracetamol) is recommended. Additional treatment with bronchodilators or IV saline may be indicated. 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. Most patients who have experienced non-life threatening infusion-related reactions have been able to complete the full course of rituximab therapy. Further treatment of patients after complete resolution of signs and symptoms has rarely resulted in repeated severe infusion-related reactions.

Patients with a high number (> 25 x 10^9/L) of circulating malignant cells or high tumour burden such as patients with CLL and mantle cell lymphoma, who may be at higher risk of especially severe infusion-related reactions, should only be treated with extreme caution and when other therapeutic alternatives have been exhausted. These patients should be very closely monitored throughout the first infusion. Consideration should be given to the use of a reduced infusion rate for the first infusion in these patients, or a split dosing over two days during the first cycle and any subsequent cycles if the lymphocyte count is still > 25 x 10^9/L.

Hypersensitivity Reactions/Anaphylaxis

Anaphylactic and other hypersensitivity reactions have been reported following the intravenous administration of proteins to patients. Adrenaline, antihistamines and corticosteroids should be available for immediate use in the event of a hypersensitivity reaction to rituximab.

Pulmonary events

Pulmonary events have included hypoxia, lung infiltration, and acute respiratory failure. Some of these events have been preceded by severe bronchospasm and dyspnoea. In some cases, symptoms worsened over time, while in others initial improvement was followed by clinical deterioration. Therefore, patients experiencing pulmonary events or other severe infusion-related symptoms should be closely monitored until complete resolution of their symptoms occurs. 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. Acute respiratory failure may be accompanied by events such as pulmonary interstitial infiltration or oedema, visible on a chest x-ray. The syndrome usually manifests itself within one or two hours of initiating the first IV infusion. Patients who experience severe pulmonary events should have their infusion interrupted immediately (see Section 4.2) and should receive aggressive symptomatic treatment.

Rapid Tumour Lysis

Rituximab mediates the rapid lysis of benign and malignant CD20-positive cells. Signs and symptoms (e.g. hyperuricaemia, hyperkalaemia, hypocalcaemia, acute renal failure, elevated LDH) consistent with tumour lysis syndrome (TLS) have been reported to occur after the first rituximab infusion in patients with high numbers of circulating malignant lymphocytes. Prophylaxis for TLS should be considered for patients at risk of developing rapid tumour lysis (e.g. patients with a high tumour burden or with a high number (> 25 x 10^9/L) of circulating malignant cells such as patients with CLL and mantle cell lymphoma). These patients should be followed closely and appropriate laboratory monitoring performed. Appropriate medical therapy should be provided for patients who develop signs and symptoms consistent with rapid tumour lysis. Following treatment for and complete resolution of signs and symptoms, subsequent rituximab therapy has been administered in conjunction with prophylactic therapy for TLS in a limited number of cases.

Cardiac disorders

Since hypotension may occur during rituximab infusion, consideration should be given to withholding antihypertensive medications 12 hours prior to and throughout rituximab infusion. Angina pectoris or

cardiac arrhythmia, such as atrial flutter and fibrillation, heart failure or myocardial infarction have occurred in patients treated with rituximab. Therefore patients with a history of cardiac disease should be monitored closely.

Monitoring of Blood Counts

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

Consideration should be given to the need for regular full blood counts, including platelet counts, during monotherapy with rituximab. When rituximab is given in combination with CHOP or CVP chemotherapy, regular full blood counts should be performed according to usual medical practice.

Infections

Rituximab treatment should not be initiated in patients with severe active infections.

Hepatitis B infections

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.

Progressive Multifocal Leucoencephalopathy

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. Physicians treating patients with NHL or CLL should consider PML in the differential diagnosis of patients reporting neurological symptoms and consultation with a Neurologist should be considered as clinically indicated.

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, 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 titre). 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.

Rheumatoid arthritis, granulomatosis with polyangiitis and microscopic polyangiitis

Methotrexate (MTX) naïve populations with rheumatoid arthritis

The use of rituximab is not recommended in MTX-naïve patients since a favourable benefit risk relationship has not been established.

Infusion related reactions

Rituximab is associated with infusion related reactions (IRRs), which may be related to release of cytokines and/or other chemical mediators. The most common symptoms were allergic reactions like headache, pruritus, throat irritation, flushing, rash, urticaria, hypertension, and pyrexia.

For RA patients, premedication consisting of an analgesic/anti-pyretic medicinal product and an anti-histaminic medicinal product, should always be administered before each infusion of rituximab. Premedication with glucocorticoids should also be administered before each infusion of rituximab in order to reduce the frequency and severity of IRRs (see Section 4.2 and Section 4.8).

For RA patients, most infusion-related events reported in clinical trials were mild to moderate in severity. Fewer than 1% of the patients experienced serious IRRs, with most of these reported during the first infusion of the first course (see Section 4.8). Severe IRRs with fatal outcome have been reported in rheumatoid arthritis patients in the post-marketing setting. Closely monitor patients with pre-existing cardiac conditions and those who experienced prior cardiopulmonary adverse reactions. 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. 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.

Hypersensitivity Reactions/ Anaphylaxis

Anaphylactic and other hypersensitivity reactions have been reported following the intravenous administration of proteins to patients. 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.

For GPA and MPA patients, IRRs were similar to those seen for RA patients in clinical trials (see Section 4.8). For GPA and MPA patients, rituximab was given in combination with high doses of glucocorticoids (see Section 4.2), which may reduce the incidence and severity of these events (see information for RA indication above).

Cardiac disorders

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 ischaemic 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.

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.

Hepatitis B Infections

Cases of hepatitis B reactivation, including those with a fatal outcome, have been reported in rheumatoid arthritis, granulomatosis with polyangiitis and microscopic polyangiitis 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.

Progressive Multifocal Leukoencephalopathy (PML)

Cases of PML have been reported following use of rituximab for the treatment of autoimmune diseases including RA, GPA and MPA. Fatal outcome has been reported in auto-immune indications. Several, but not all of the reported cases had potential risk factors for PML, including the underlying disease, long-term immunosuppressive therapy or chemotherapy. PML has also been reported in patients with autoimmune disease not treated with rituximab. Physicians treating patients with

autoimmune disease should consider PML in the differential diagnosis of patients reporting neurological symptoms and consultation with a neurologist should be considered as clinically indicated.

Immunisation

Physicians should review the patient's vaccination status and patients should, if possible, be brought up to date with all immunisations in alignment with current immunisation guidelines prior to 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 viral 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.

Paediatric use

The safety and effectiveness of rituximab in paediatric patients have not been established.

Hypogammaglobulinaemia has 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.

Concomitant/sequential use of other DMARDs in rheumatoid arthritis

The concomitant use of rituximab and anti-rheumatic therapies other than those specified under the rheumatoid arthritis indication and posology is not recommended.

There are limited data from clinical trials to fully assess the safety of the sequential use of other DMARDs (including TNF inhibitors and other biologics) following rituximab (see Section 4.5). The available data indicate that the rate of clinically relevant infection is unchanged when such therapies are used in patients previously treated with rituximab, however patients should be closely observed for signs of infection if biologic agents and/or DMARDs are used following rituximab therapy.

Malignancy

Immunomodulatory medicinal products may increase the risk of malignancy. On the basis of limited experience with rituximab in rheumatoid arthritis patients (see Section 4.8) the present data do not seem to suggest any increased risk of malignancy. However, the possible risk for the development of solid tumours cannot be excluded at this time.

4.5 Interaction with other medicines and other forms of interaction

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

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

Co-administration with methotrexate had no effect on the pharmacokinetics of rituximab in rheumatoid arthritis patients.

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

In patients with rheumatoid arthritis, 283 patients received subsequent therapy with a biologic DMARD following rituximab. In these patients the rate of clinically relevant infection while on rituximab was 6.01 per 100 patient years compared to 4.97 per 100 patient years following treatment with the biologic DMARD.

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. Similar effects have been observed in animal studies (see section 5.3). 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 rituximab concentrations in milk (relative infant dose less than 0.4%). In the few cases where breastfed infants were followed-up, infants showed normal growth and development up to 2 years. However, as these data are limited and the long-term outcomes of breastfed infants remain unknown, breast-feeding is not recommended while being treated with Riximyo and, optimally, also for 6 months following Riximyo treatment.

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

Summary of the safety profile

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

The most frequently observed adverse drug 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 frequent reported or observed serious adverse drug reactions were:

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

• Infections, see Section 4.4.

• Cardiovascular events, see Section 4.4.

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

List of adverse reactions

The frequencies of ADRs reported with rituximab alone or in combination with chemotherapy are summarised below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1000), very rare (< 1/10,000) and not known (cannot be estimated from the available data).

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

ADRs reported in clinical trials or during postmarketing surveillance in patients with NHL and CLL disease treated with rituximab monotherapy/maintenance or in combination with chemotherapy.

Infections and infestations

Very common:	Bacterial infections, viral infections, [+]bronchitis
Common:	Sepsis, [+]pneumonia, [+]febrile infection, [+]herpes zoster, [+]respiratory tract infection, fungal infections, infections of unknown aetiology, [+]acute bronchitis, [+]sinusitis, hepatitis B[1]
Rare:	Serious viral infection[2], Pneumocystis jirovecii
Very rare:	PML

Blood and lymphatic system disorders

Very common:	Neutropenia, leucopenia, [+]febrile neutropenia, [+]thrombocytopenia
Common:	Anaemia, thrombocytopenia, [+]pancytopenia, [+]granulocytopenia
Uncommon:	Coagulation disorders, aplastic anaemia, haemolytic anaemia, lymphadenopathy
Very rare:	Transient increase in serum IgM levels[3]
Not known:	Late neutropenia[3]

Immune system disorders

Very common:	Infusion related reactions[4], angioedema
Common:	Hypersensitivity
Rare:	Anaphylaxis
Very rare:	Tumour lysis syndrome, cytokine release syndrome[4], serum sickness
Not known:	Infusion-related acute reversible thrombocytopenia[4]

Metabolism and nutrition disorders

Common:	Hyperglycaemia, weight decrease, peripheral oedema, face oedema, increased LDH, hypocalcaemia

Psychiatric disorders

Uncommon:	Depression, nervousness

Nervous system disorders

Common:	Paraesthesia, hypoaesthesia, agitation, insomnia, vasodilatation, dizziness, anxiety
Uncommon:	Dysgeusia
Very rare:	Peripheral neuropathy, facial nerve palsy[5]
Not known:	Cranial neuropathy, loss of other senses[5]

Eye disorders

Common:	Lacrimation disorder, conjunctivitis
Very rare:	Severe vision loss[5]

Ear and labyrinth disorders

Common:	Tinnitus, ear pain
Not known:	Hearing loss[5]

Cardiac disorders

Common:	[+]Myocardial infarction[4,6], arrhythmia, [+]atrial fibrillation, tachycardia, [+]cardiac disorder
Uncommon:	[+]Left ventricular failure, [+]supraventricular tachycardia, [+]ventricular tachycardia, [+]angina, [+]myocardial ischaemia, bradycardia
Rare:	Severe cardiac disorders[4,6]
Very rare:	Heart failure[4,6]

Vascular disorders

Common:	Hypertension, orthostatic hypotension, hypotension
Very rare:	Vasculitis (predominately cutaneous), leukocytoclastic vasculitis

Respiratory, thoracic and mediastinal disorders

Common:	Bronchospasm[4], respiratory disease, chest pain, dyspnoea, increased cough, rhinitis
Uncommon:	Asthma, bronchiolitis obliterans, lung disorder, hypoxia
Rare:	Interstitial lung disease[7]
Very rare:	Respiratory failure[4]
Not known:	Lung infiltration

Gastrointestinal disorders

Very common:	Nausea
Common:	Vomiting, diarrhoea, abdominal pain, dysphagia, stomatitis, constipation, dyspepsia, anorexia, throat irritation
Uncommon:	Abdominal enlargement
Very rare:	Gastrointestinal perforation[7]

Skin and subcutaneous tissue disorders

Very common:	Pruritus, rash, [+]alopecia
Common:	Urticaria, sweating, night sweats, [+]skin disorder, [+]alopecia
Very rare:	Severe bullous skin reactions, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome)[7]

Musculoskeletal, connective tissue and bone disorders

Common:	Hypertonia, myalgia, arthralgia, back pain, neck pain, pain

Renal and urinary disorders

Very rare:	Renal failure[4]

General disorders and administration site conditions

Very common:	Fever, chills, asthenia, headache
Common:	Tumour pain, flushing, malaise, cold syndrome, [+]fatigue, [+]shivering, [+]multi-organ failure[4]
Uncommon:	Infusion site pain

Investigations

Very common:	Decreased IgG levels

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

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

[2] see also section infection below

[3] see also section haematologic adverse reactions below

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

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

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

[7] includes fatal cases

The following terms have been reported as adverse events during clinical trials, however, were reported at a similar or lower incidence in the rituximab arms compared to control arms: 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 haematopoetic stem cell transplant. Examples of these serious viral infections are infections caused by the herpes viruses (Cytomegalovirus, Varicella Zoster Virus and Herpes Simplex Virus), JC virus (progressive multifocal leukoencephalopathy (PML)) and hepatitis C virus. Cases of fatal PML that occurred after disease progression and retreatment have also been reported in clinical trials. Cases of hepatitis B reactivation, have been reported, the majority of which were in 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 $1x10^9$/L between day 24 and 42 after the last dose) or occurred with a late onset (defined as neutrophil count below $1x10^9$/L later than 42 days after last dose in patients with no previous prolonged neutropenia or who recovered prior to day 42) following treatment with rituximab plus FC. There were no differences reported for the incidence of anaemia. Some cases of late neutropenia occurring more than four weeks after the last infusion of rituximab were reported. In the CLL first-line study, Binet stage C patients experienced more adverse events in the R-FC arm compared to the FC arm (R-FC 83% vs. FC 71%). In the relapsed/refractory CLL study grade ¾ 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 patients (≥ 65 years)

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

Bulky disease

There was a higher incidence of grade 3/4 ADRs in patients with bulky disease than in patients without bulky disease (25.6% vs. 15.4%). The incidence of ADRs of any grade was similar in these two groups.

Re-treatment

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

Patient subpopulations - rituximab combination therapy

Elderly patients (≥ 65 years)

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

Experience from rheumatoid arthritis

Summary of the safety profile

The overall safety profile of rituximab in rheumatoid arthritis is based on data from patients from clinical trials and from post-marketing surveillance.

The safety profile of rituximab in patients with moderate to severe rheumatoid arthritis (RA) is summarised in the sections below. In clinical trials more than 3100 patients received at least one treatment course and were followed for periods ranging from 6 months to over 5 years; approximately 2400 patients received two or more courses of treatment with over 1000 having received 5 or more courses. The safety information collected during post-marketing experience reflects the expected adverse reaction profile as seen in clinical trials for rituximab (see Section 4.4).

Patients received 2 x 1000 mg of rituximab separated by an interval of two weeks; in addition to methotrexate (10-25 mg/week). Rituximab infusions were administered after an intravenous infusion of 100 mg methylprednisolone; patients also received treatment with oral prednisone for 15 days.

List of adverse reactions

Adverse reactions are listed below. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), and very rare (< 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The most frequent adverse reactions considered due to receipt of rituximab were IRRs. The overall incidence of IRRs in clinical trials was 23% with the first infusion and decreased with subsequent infusions. Serious IRRs were uncommon (0.5% of patients) and were predominantly seen during the initial course. In addition to adverse reactions seen in RA clinical trials for rituximab, progressive

multifocal leukoencephalopathy (PML) (see Section 4.4) and serum sickness-like reaction have been reported during post marketing experience.

Summary of adverse drug reactions reported in clinical trials or during postmarketing surveillance occurring in patients with rheumatoid arthritis receiving rituximab

Infections and infestations

Very common: Upper respiratory tract infection, urinary tract infections

Common: Bronchitis, sinusitis, gastroenteritis, tinea pedis

Very rare: PML, reactivation of hepatitis B

Other serious viral infections, some of which were fatal, have been reported in patients treated with rituximab.

Blood and lymphatic system disorders

Common: Neutropenia[1]

Rare: Late neutropenia[2]

Very rare: Serum sickness-like reaction

Immune system disorders

Very common: [3]Infusion related reactions (hypertension, nausea, rash, pyrexia, pruritus, urticaria, throat irritation, hot flush, hypotension, rhinitis, rigors, tachycardia, fatigue, oropharyngeal pain, peripheral oedema, erythema)

Uncommon: [3]Infusion related reactions (generalised oedema, bronchospasm, wheezing, laryngeal oedema, angioneurotic oedema, generalised pruritus, anaphylaxis, anaphylactoid reaction)

Metabolism and nutrition disorders

Common: Hypercholesterolaemia

Psychiatric disorders

Common: Depression, anxiety

Nervous system disorders

Very common: Headache

Common: Paraesthesia, migraine, dizziness, sciatia

Cardiac disorders

Rare: Angina pectoris, atrial fibrillation, heart failure, myocardial infarction

Very rare: Atrial flutter

Gastrointestinal disorders

Common: Dyspepsia, diarrhoea, gastro-oesophageal reflux, mouth ulceration, upper abdominal pain

Skin and subcutaneous tissue disorders

Common: Alopecia

Very rare: Toxic epidermal necrolysis (Lyell's syndrome), Stevens-Johnson syndrome[5]

Musculoskeletal, connective tissue and bone disorders

Common: Arthralgia / musculoskeletal pain, osteoarthritis, bursitis

Investigations

Very common: Decreased IgM levels[4]

Common: Decreased IgG levels[4]

[1] Frequency category derived from laboratory values collected as part of routine laboratory monitoring in clinical trials

[2] Frequency category derived from post-marketing data.

[3] Reactions occurring during or within 24 hours of infusion. See also infusion-related reactions below. IRRs may occur as a result of hypersensitivity and/or to the mechanism of action.

[4] Includes observations collected as part of routine laboratory monitoring.

[5] Includes fatal cases

Multiple courses

Multiple courses of treatment are associated with a similar ADR profile to that observed following first exposure. The rate of all ADRs following first rituximab exposure was highest during the first 6 months and declined thereafter. This is mostly accounted for by IRRs (most frequent during the first treatment course), RA exacerbation and infections, all of which were more frequent in the first 6 months of treatment.

Infusion-related reactions

The most frequent ADRs following receipt of rituximab in clinical studies were IRRs (see above). Among the 3189 patients treated with rituximab, 1135 (36%) experienced at least one IRR with 733/3189 (23%) of patients experiencing an IRR following first infusion of the first exposure to rituximab. The incidence of IRRs declined with subsequent infusions. In clinical trials fewer than 1% (17/3189) of patients experienced a serious IRR. There were no CTC Grade 4 IRRs and no deaths due to IRRs in the clinical trials. The proportion of CTC Grade 3 events and of IRRs leading to withdrawal decreased by course and were rare from course 3 onwards. Premedication with intravenous glucocorticoid significantly reduced the incidence and severity of IRRs (see Section 4.2 and Section 4.4). Severe IRRs with fatal outcome have been reported in the post-marketing setting.

In a trial designed to evaluate the safety of a more rapid rituximab infusion in patients with rheumatoid arthritis, patients with moderate-to-severe active RA who did not experience a serious IRR during or within 24 hours of their first studied infusion were allowed to receive a 2-hour intravenous infusion of rituximab. Patients with a history of a serious infusion reaction to a biologic therapy for RA were excluded from entry. The incidence, types and severity of IRRs were consistent with that observed historically. No serious IRRs were observed.

Description of selected adverse reactions

Infections

The overall rate of infection was approximately 94 per 100 patient years in rituximab treated patients. The infections were predominately mild to moderate and consisted mostly of upper respiratory tract infections and urinary tract infections. The incidence of infections that were serious or required IV antibiotics was approximately 4 per 100 patient years. The rate of serious infections did not show any significant increase following multiple courses of rituximab. Lower respiratory tract infections (including pneumonia) have been reported during clinical trials, at a similar incidence in the rituximab arms compared to control arms.

Cases of progressive multifocal leukoencephalopathy with fatal outcome have been reported following use of rituximab for the treatment of autoimmune diseases. This includes rheumatoid arthritis and off-label autoimmune diseases, including Systemic Lupus Erythematosus (SLE) and vasculitis.

In patients with non-Hodgkin's lymphoma receiving rituximab in combination with cytotoxic chemotherapy, cases of hepatitis B reactivation have been reported (see non-Hodgkin's lymphoma). Reactivation of hepatitis B infection has also been very rarely reported in RA patients receiving rituximab (see Section 4.4).

Cardiovascular adverse reactions

Serious cardiac reactions were reported at a rate of 1.3 per 100 patient years in the rituximab treated patients compared to 1.3 per 100 patient years in placebo treated patients. The proportions of patients experiencing cardiac reactions (all or serious) did not increase over multiple courses.

Neurologic events

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.

Neutropenia

Events of neutropenia were observed with rituximab treatment, the majority of which were transient and mild or moderate in severity. Neutropenia can occur several months after the administration of rituximab (see Section 4.4).

In placebo-controlled periods of clinical trials, 0.94% (13/1382) of rituximab treated patients and 0.27% (2/731) of placebo patients developed severe neutropenia.

Neutropenic events, including severe late onset and persistent neutropenia, have been rarely reported in the post-marketing setting, some of which were associated with fatal infections.

Skin and subcutaneous tissue disorders

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

Laboratory abnormalities

Hypogammaglobulinaemia (IgG or IgM below the lower limit of normal) has been observed in RA patients treated with rituximab. There was no increased rate in overall infections or serious infections after the development of low IgG or IgM (see Section 4.4).

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.

Experience from granulomatosis with polyangiitis and microscopic polyangiitis

In the clinical trial in granulomatosis with polyangiitis and microscopic polyangitis, 99 patients were treated with rituximab (375 mg/m^2, once weekly for 4 weeks) and glucocorticoids (see Section 5.1).

Tabulated list of adverse reactions

The ADRs listed in Table 1 were all adverse events which occurred at an incidence of ≥ 5% in the rituximab group.

Table 1 Adverse drug reactions occurring at 6-months in ≥ 5% of patients receiving rituximab, and at a higher frequency than the comparator group, in the pivotal clinical study.

Body system **Adverse event**	**Rituximab (n=99)**
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%
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%

Selected adverse drug reactions

Infusion related reactions

IRRs in the GPA and MPA clinical trial 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. Ninety-nine patients were treated with rituximab and 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 the 99 rituximab patients, 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%.

Malignancies

The incidence of malignancy in rituximab treated patients in the granulomatosis with polyangiitis and microscopic polyangiitis clinical study was 2.00 per 100 patient years at the study common closing date (when the final patient had completed the follow-up period). On the basis of standardized incidence ratios, the incidence of malignancies appears to be similar to that previously reported in patients with ANCA-associated vasculitis.

Cardiovascular adverse reactions

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 granulomatosis with polyangiitis and microscopic polyangiitis patients treated with rituximab. At 6 months, in the active-controlled, randomised, double-blind, multicentre, non-inferiority trial, 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. There was no increased rate in overall infections or serious infections in patients with low IgA, IgG or IgM.

Neutropenia

In the active-controlled, randomised, double-blind, multicentre, non-inferiority trial of rituximab in granulomatosis with polyangiitis and microscopic polyangiitis, 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. The effect of multiple rituximab courses on the development of neutropenia in granulomatosis with polyangiitis and microscopic polyangiitis patients has not been studied in clinical trials.

Skin and subcutaneous tissue disorders

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring od the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions
https://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose

Limited experience with doses higher than the approved dose of intravenous rituximab formulation is available from clinical trials in humans. The highest intravenous dose of rituximab tested in humans to date is 5000 mg (2250 mg/m^2), tested in a dose escalation study in patients with CLL. No additional safety signals were identified. Patients who experience overdose should have immediate interruption of their infusion and be closely monitored. 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.

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

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents, monoclonal antibodies

ATC code: L01FA01

RIXIMYO® is a biosimilar medicinal product.

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

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

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

Peripheral B cell counts declined below normal following completion of the first dose of rituximab. In patients treated for haematological malignancies, B cell recovery began within 6 months of treatment and generally returned to normal levels within 12 months after completion of therapy, although in some patients this may take longer (up to a median recovery time of 23 months post-induction therapy). In rheumatoid arthritis patients, immediate depletion of B cells in the peripheral blood was observed following two infusions of 1,000 mg rituximab separated by a 14 day interval. Peripheral blood B cell counts begin to increase from week 24 and evidence for repopulation is observed in the majority of patients by week 40, whether rituximab was administered as monotherapy or in combination with methotrexate. A small proportion of patients had prolonged peripheral B cell depletion lasting 2 years or more after their last dose of rituximab. In patients with granulomatosis with polyangiitis or microscopic polyangiitis, the number of peripheral blood B cells decreased to < 10 cells/µl after two weekly infusions of rituximab 375 mg/m^2, and remained at that level in most patients up to the 6 month time point. The majority of patients (81%) showed signs of B cell return, with counts > 10 cells/µl by month 12, increasing to 87% of patients by month 18.

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 375 mg/m^2 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% (CI 95% 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/m^2 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/m^2 of rituximab as intravenous infusion weekly for four doses. The ORR was 36% (CI 95% 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/m^2 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% (CI 95% 26% – 51%; CR 10%, PR 28%) 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/m^2, vincristine 1.4 mg/m^2 up to a maximum of 2 mg on day 1, and prednisolone 40 mg/m^2/day on days 1 - 5) every 3 weeks for 8 cycles or rituximab 375 mg/m^2 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. Key results from all four studies are summarised in Table 2.

Table 2 Summary of key results from four phase III randomised studies evaluating the benefit of rituximab with different chemotherapy regimens in follicular lymphoma

Study	Treatment, n	Median FU, months	ORR, %	CR, %	Median TTF?PFS/EFS mo	OS rates, %
M39021	CVP, 159 R-CVP, 162	53	57 81	10 41	Median TTP: 14.7 33.6 p < 0.0001	53-months 71.1 80.9 p=0.029
GLSG'00	CHOP, 205 R-CHOP, 223	18	90 96	17 20	Median TTF: 2.6 years Not reached p < 0.001	18-months 90 95 p=0.016
OSHO_39	MCP, 96 R-MCP, 105	47	75 92	25 50	Median PFS: 28.8 Not reached p < 0.0001	48-months 74 87 p=0.0096
FL2000	CHVP-IFN, 183 R-CHVP-IFN, 175	42	85 94	49 76	Median EFS: 36 Not reached p < 0.0001	42-months 84 91 p=0.029

EFS – Event Free Survival
TTP – Time to progression or death
PFS – Progression-Free Survival
TTF – Time to Treatment Failure
OS rates – survival rates at the time of the analyses

Maintenance therapy

Previously untreated follicular lymphoma:
In a prospective, open label, international, multi-centre, phase III trial 1,193 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 1,078 patients responded to induction therapy, of which 1,018 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/m^2 body surface area given every 2 months until disease progression or for a maximum period of two years.

After a median observation time of 25 months from randomisation, 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 (Table 3).

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) (Table 3). The results of the primary analysis were confirmed with longer follow-up (median observation time: 48 months and 73 months), and have been added to Table 3 to show the comparison between the 25 and 48 and 73 month follow up periods.

Table 3 Maintenance phase: overview of efficacy results rituximab vs. observation after 73 months median observation time (compared with results of primary analysis based on 25 months median observation time, and updated analysis based on 48 months median observation time)

	Observation n=513	**Rituximab n=505**	**Log-rank p value**	**Risk reduction**
Primary efficacy				
PFS (median)	48.5 months [48.4 months] (NR)	NR [NR] (NR)	< 0.0001 [< 0.0001] (< 0.0001)	42% [45%] (50%)
Secondary efficacy				
EFS (median)	48.4 months [47.6 months] (37.8 months)	NR [NR] (NR)	< 0.0001 [< 0.0001] (< 0.0001)	39% [42%] (46%)
OS (median)	NR [NR] (NR)	NR [NR] (NR)	0.8959 [0.9298] (0.7246)	-2% [-2%] (11%)
TNLT (median)	71.0 months [60.2 months] (NR)	NR [NR] (NR)	< 0.0001 [< 0.0001] (0.0003)	37% [39%] (39%)
TNCT (median)	85.1 months [NR] (NR)	NR [NR] (NR)	0.0006 [0.0006] (0.0011)	30% [34%] (40%)
ORR*	60.7% [60.7%] (55.0%)	79.0% [79.0%] (74.0%)	< 0.0001# [< 0.0001#] (< 0.0001)	OR=2.43 [OR=2.43] (OR=2.33)
Complete response (CR/CRu) rate*	52.7% [52.7%] (47.7%)	66.8% [72.2%] (66.8%)	< 0.0001 [< 0.0001] (< 0.0001)	OR=2.34 [OR=2.34] (OR=2.21)

* At end of maintenance/observation; # p values from chi-squared test.

Main values correspond to 73 months median observation time, italicised values in brackets correspond to 48 months median observation time, and values in parentheses correspond to 25 months median observation time (primary analysis). PFS: progression-free survival; EFS: event-free survival; OS: overall survival; TNLT: time to next anti-lymphoma treatment; TNCT: time to next chemotherapy treatment; ORR: overall response rate; NR: not reached at time of clinical cut-off, OR: odds ratio.

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/m^2 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 (see Table 4).

Table 4 Induction phase: overview of efficacy results for CHOP vs. R-CHOP (31 months median observation time)

	CHOP	R-CHOP	p-value	Risk reduction[1]
Primary Efficacy				
ORR[2]	74%	87%	0.0003	N/A
CR[2]	16%	29%	0.0005	N/A
PR[2]	58%	58%	0.9449	N/A

[1] Estimates were calculated by hazard ratios
[2] Last tumour response as assessed by the investigator. The “primary” statistical test for “response” was the trend test of CR versus PR versus non-response ($p < 0.0001$)
Abbreviations: NA, not available; ORR: overall response rate; CR: complete response; PR: partial response

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%).

Table 5 Maintenance phase: overview of efficacy results rituximab vs. observation (28 months median observation time)

Efficacy parameter	Kaplan-Meier estimate of median time to event (months)			Risk Reduction
	Observation (n=167)	Rituximab (n=167)	Log-rank p-value	
Progression-free survival (PFS)	14.3	42.2	< 0.0001	61%
Overall Survival	NR	NR	0.0039	56%
Time to new lymphoma treatment Disease-free survivala	20.1 16.5	38.8 53.7	< 0.0001 0.0003	50% 67%
Subgroup analysis PFS				
CHOP	11.6	37.5	< 0.0001	71%
R-CHOP	22.1	51.9	0.0071	46%
CR	14.3	52.8	0.0008	64%
PR	14.3	37.8	< 0.0001	54%
OS				
CHOP	NR	NR	0.0348	55%
R-CHOP	NR	NR	0.0482	56%

NR: not reached; a: only applicable to patients achieving a CR

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 5). 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.

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/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2 up to a maximum of 2 mg on day 1, and prednisolone 40 mg/m^2/day on days 1-5) every 3 weeks for eight cycles, or rituximab 375 mg/m^2 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 patients subgroups (gender, age, age adjusted IPI, Ann Arbor stage, ECOG, β2 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 HACA, 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/m^2, days 1-3) every 4 weeks for 6 cycles or rituximab in combination with FC (R-FC). Rituximab was administered at a dose of 375 mg/m^2 during the first cycle one day prior to chemotherapy and at a dose of 500 mg/m^2 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 (Table 6a and Table 6b) and 552 patients (276 R-FC, 276 FC) for the relapsed/refractory study (Table 7) 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 R-FC 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) (Table 6a). 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) (Table 6b).

Table 6a First-line treatment of chronic lymphocytic leukaemia Overview of efficacy results for rituximab plus FC vs. FC alone – 48.1 months median observation time

Efficacy parameter	Kaplan-Meier estimate of median time to event (months)			Risk Reduction
	FC (n=409)	R-FC (n=409)	Log-rank p-value	
Progression-free survival (PFS)	32.8	55.3	< 0.0001	45%
Overall Survival	NR	NR	0.0319	27%
Event free survival	31.3	51.8	< 0.0001	44%
Response rate (CR, nPR, or PR) CR rates	72.6% 16.9%	85.8% 36.0%	< 0.0001 < 0.0001	n.a. n.a.
Duration of response*	36.2	57.3	< 0.0001	44%
Disease free survival (DFS)**	48.9	60.3	0.0520	31%
Time to new treatment	47.2	69.7	<0.0001	42%

Response rate and CR rates analysed using Chi-squared Test. NR: not reached; n.a.: not applicable
*: only applicable to patients achieving a CR, nPR, PR
**: only applicable to patients achieving a CR

Table 6b First-line treatment of chronic lymphocytic leukaemia Hazard ratios of progression-free survival according to Binet stage (ITT) – 48.1 months median observation time

Progression-free survival (PFS)	Number of patients		Hazard ratio (95% CI)	p-value (Wald test, not adjusted)
	FC	R-FC		
Binet stage A	22	18	0.39 (0.15; 0.98)	0.0442
Binet stage B	259	263	0.52 (0.41; 0.66)	<0.0001
Binet stage C	126	126	0.68 (0.49; 0.95)	0.0224

CI: Confidence Interval

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

Table 7 Treatment of relapsed/refractory chronic lymphocytic leukaemia - overview of efficacy results for rituximab plus FC vs. FC alone (25.3 months median observation time)

Efficacy parameter	Kaplan-Meier estimate of median time to event (months)			Risk reduction
	FC (n=276)	R-FC (n=276)	Log-rank p value	
Progression-free survival (PFS)	20.6	30.6	0.0002	35%
Overall survival	51.9	NR	0.2874	17%
Event free survival	19.3	28.7	0.0002	36%
Response rate (CR, nPR, or PR)	58.0%	69.9%	0.0034	n.a.
CR rates	13.0%	24.3%	0.0007	n.a.
Duration of response*				
Disease free survival (DFS)**	27.6	39.6	0.0252	31%
Time to new CLL treatment	42.2	39.6	0.8842	-6%
	34.2	NR	0.0024	35%

Response rate and CR rates analysed using Chi-squared Test.
*: only applicable to patients achieving a CR, nPR, PR; NR: not reached; n.a. not applicable
**: only applicable to patients achieving a CR;

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.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with rituximab in all subsets of the paediatric population with follicular lymphoma and chronic lymphocytic leukaemia. See Section 4.2 for information on paediatric use.

Clinical experience in rheumatoid arthritis

The efficacy and safety of rituximab in alleviating the symptoms and signs of rheumatoid arthritis in patients with an inadequate response to TNF-inhibitors was demonstrated in a pivotal randomised, controlled, double-blind, multicentre trial (Trial 1).

Trial 1 evaluated 517 patients that had experienced an inadequate response or intolerance to one or more TNF inhibitor therapies. Eligible patients had active rheumatoid arthritis, diagnosed according to the criteria of the American College of Rheumatology (ACR). Rituximab was administered as two intravenous infusions separated by an interval of 15 days. Patients received 2 x 1,000 mg intravenous infusions of rituximab or placebo in combination with MTX. All patients received concomitant 60 mg oral prednisone on days 2-7 and 30 mg on days 8-14 following the first infusion. The primary endpoint was the proportion of patients who achieved an ACR20 response at week 24. Patients were followed beyond week 24 for long term endpoints, including radiographic assessment at 56 weeks and at 104 weeks. During this time, 81% of patients, from the original placebo group received rituximab between weeks 24 and 56, under an open label extension study protocol.

Trials of rituximab in patients with early arthritis (patients without prior methotrexate treatment and patients with an inadequate response to methotrexate, but not yet treated with TNF-alpha inhibitors) have met their primary endpoints. Rituximab is not indicated for these patients, since the safety data about long-term rituximab treatment are insufficient, in particular concerning the risk of development of malignancies and PML.

Disease activity outcomes

Rituximab in combination with methotrexate significantly increased the proportion of patients achieving at least a 20% improvement in ACR score compared with patients treated with methotrexate alone (Table 8). Across all development studies the treatment benefit was similar in patients independent of age, gender, body surface area, race, number of prior treatments or disease status.

Clinically and statistically significant improvement was also noted on all individual components of the ACR response (tender and swollen joint counts, patient and physician global assessment, disability index scores (HAQ), pain assessment and C-Reactive Proteins (mg/dl).

Table 8 Clinical response outcomes at primary endpoint in Trial 1 (ITT population)

	Outcome†	**Placebo+MTX**	**Rituximab+MTX (2 x 1,000 mg)**
Trial 1	ACR20 ACR50 ACR70	36 (18%) 11 (5%) 3 (1%)	153 (51%)*** 80 (27%)*** 37 (12%)***
	EULAR response (good/moderate)	44 (22%)	193 (65%)***
	Mean change in DAS	-0.34	-1.83***

† Outcome at 24 weeks
Significant difference from placebo + MTX at the primary timepoint: ***p ≤ 0.0001

Patients treated with rituximab in combination with methotrexate had a significantly greater reduction in disease activity score (DAS28) than patients treated with methotrexate alone (Table 8). Similarly, a good to moderate European League Against Rheumatism (EULAR) response was achieved by significantly more rituximab treated patients treated with rituximab and methotrexate compared to patients treated with methotrexate alone (Table 8).

Radiographic response

Structural joint damage was assessed radiographically and expressed as change in modified Total Sharp Score (mTSS) and its components, the erosion score and joint space narrowing score.

In Trial 1, conducted in patients with inadequate response or intolerance to one or more TNF inhibitor therapies, receiving rituximab in combination with methotrexate demonstrated significantly less radiographic progression than patients originally receiving methotrexate alone at 56 weeks. Of the patients originally receiving methotrexate alone, 81% received rituximab either as rescue between weeks 16-24 or in the extension trial, before week 56. A higher proportion of patients receiving the original rituximab/MTX treatment also had no erosive progression over 56 weeks (Table 9).

Table 9 Radiographic outcomes at 1 year (mITT population)

	Placebo+MTX	**Rituximab+MTX 2 x 1,000 mg**
Trial 1	(n=184)	(n=273)
Mean change from baseline:		
Modified total sharp score	2.30	1.01*
Erosion score	1.32	0.60*
Joint space narrowing score	0.98	0.41**
Porportion of patients with no radiographic change	46%	53%, NS
Porportion of patients with no erosive change	52%	60%, NS

150 patients originally randomised to placebo + MTX in Trial 1 received at least one course of RTX + MTX by one year * $p < 0.05$, ** $p < 0.001$. Abbreviation: NS, non-significant

Inhibition of the rate of progressive joint damage was also observed long term. Radiographic analysis at 2 years in Trial 1 demonstrated significantly reduced progression of structural joint damage in patients receiving rituximab in combination with methotrexate compared to methotrexate alone as well as a significantly higher proportion of patients with no progression of joint damage over the 2 year period.

Physical function and quality of life outcomes

Significant reductions in disability index (HAQ-DI) and fatigue (FACIT-Fatigue) scores were observed in patients treated with rituximab compared to patients treated with methotrexate alone. The proportions of rituximab treated patients showing a minimal clinically important difference (MCID) in HAQ-DI (defined as an individual total score decrease of > 0.22) was also higher than among patients receiving methotrexate alone (Table 10).

Significant improvement in health related quality of life was also demonstrated with significant improvement in both the physical health score (PHS) and mental health score (MHS) of the SF-36. Further, significantly higher proportion of patients achieved MCIDs for these scores (Table 10).

Table 10 Physical Function and Quality of Life outcomes at week 24 in Trial 1

Outcome†	**Placebo+MTX**	**Rituximab+MTX 2 x 1,000 mg**
Mean change in HAQ-DI	N=201 0.1	N=298 -0.4***
%HAQ-DI MCID	20%	51%
Mean change in FACIT-T	-0.5	-9.1***
Mean change in SF-36 PHS	N=197 0.9	N=294 5.8***
% SF-36 PHS MCID	13%	48%***
Mean change in SF-36 MHS	1.3	4.7**
% SF-36 MHS MCID	20%	38%*

† Outcome at 24 weeks

Significant difference from placebo at the primary time point: * $p < 0.05$, ** $p < 0.001$, *** $p \leq 0.0001$
MCID HAQ-DI ≥ 0.22, MCID SF-36 PHS > 5.42, MCID SF-36 MHS > 6.33

Efficacy in autoantibody (RF and or anti-CCP) seropositive patients

Patients seropositive to Rheumatoid Factor (RF) and/or anti-Cyclic Citrullinated Peptide (anti-CCP) who were treated with rituximab in combination with methotrexate showed an enhanced response compared to patients negative to both.

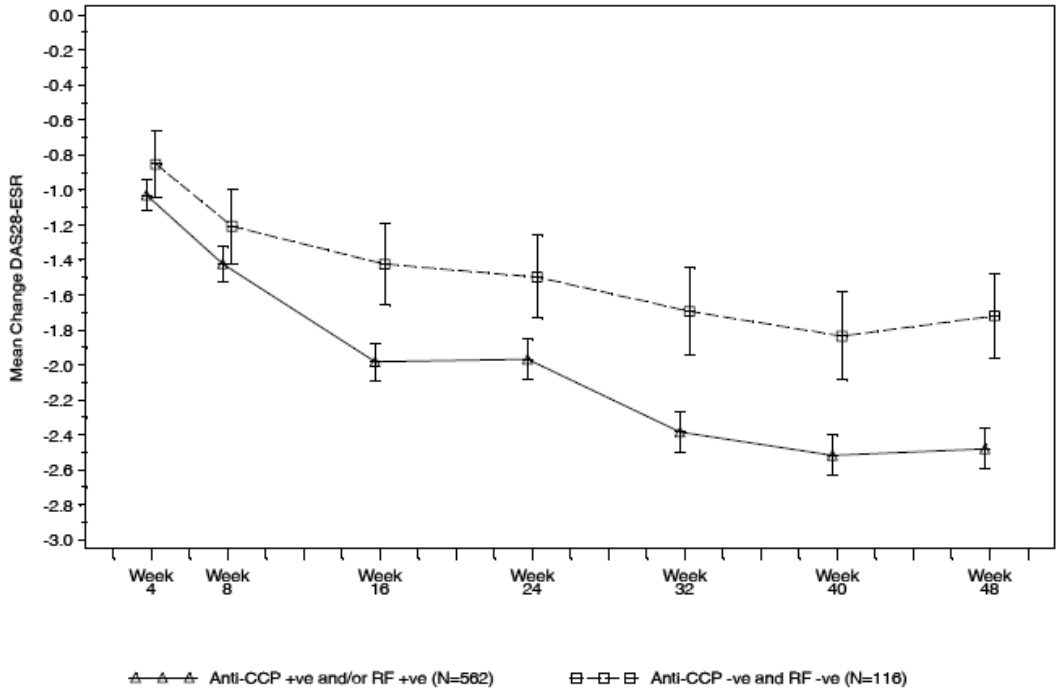
Efficacy outcomes in rituximab treated patients were analysed based on autoantibody status prior to commencing treatment. At week 24, patients who were seropositive to RF and/or anti-CCP at baseline had a significantly increased probability of achieving ACR20 and 50 responses compared to seronegative patients (p=0.0312 and p=0.0096) (Table 11). These findings were replicated at week 48, where autoantibody seropositivity also significantly increased the probability of achieving ACR70. At week 48 seropositive patients were 2-3 times more likely to achieve ACR responses compared to seronegative patients. Seropositive patients also had a significantly greater decrease in DAS28-ESR compared to seronegative patients (Figure 1).

Table 11 Summary of efficacy by baseline autoantibody status

	Week 24		**Week 48**	
	Seropositive	**Seronegative**	**Seropositive**	**Seronegative**
	(n=514)	**(n=106)**	**(n=506)**	**(n=101)**
ACR20 (%)	62.3*	50.9	71.1*	51.5
ACR50 (%)	32.7*	19.8	44.9*	22.8
ACR70 (%)	12.1	5.7	20.9*	6.9
EULAR response (%)	74.8*	62.9	84.3*	72.3
Mean change DAS28-ESR	-1.97**	-1.50	-2.48***	-1.72

Significance levels were defined as * p < 0.05, ** p < 0.001, *** p < 0.0001.

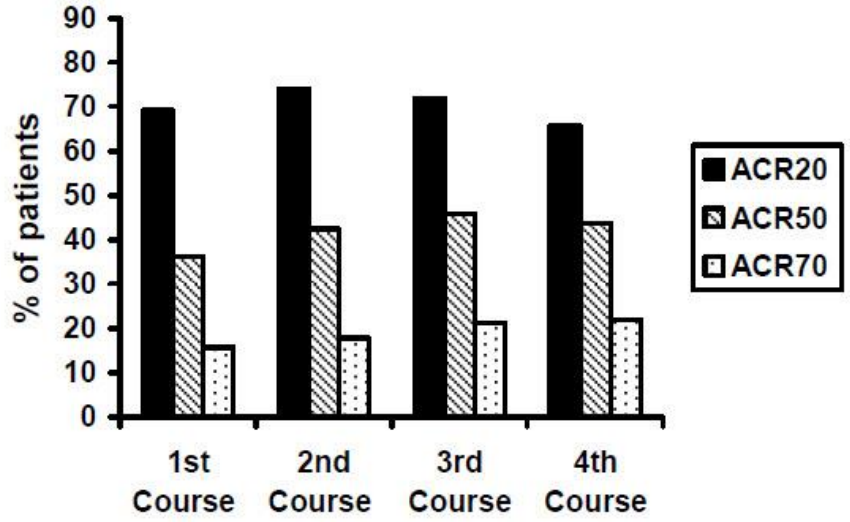
Figure 1: Change from baseline of DAS28-ESR by baseline autoantibody status



Long-term efficacy with multiple course therapy

Treatment with rituximab in combination with methotrexate over multiple courses resulted in sustained improvements in the clinical signs and symptoms of RA, as indicated by ACR, DAS28-ESR and EULAR responses which was evident in all patient populations studied (Figure 2). Sustained improvement in physical function as indicated by the HAQ-DI score and the proportion of patients achieving MCID for HAQ-DI were observed.

Figure 2: ACR responses for 4 treatment courses (24 weeks after each course (within patient, within visit) in patients with an inadequate response to TNF-inhibitors (n=146)



Clinical laboratory finding

A total of 392/3,095 (12.7%) patients with rheumatoid arthritis tested positive for HACA in clinical studies following therapy with rituximab. The emergence of HACA was not associated with clinical deterioration or with an increased risk of reactions to subsequent infusions in the majority of patients. The presence of HACA may be associated with worsening of infusion or allergic reactions after the second infusion of subsequent courses.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with rituximab in all subsets of the paediatric population with autoimmune arthritis. See Section 4.2 for information on paediatric use.

Clinical experience in granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis

A total of 197 patients aged 15 years or older with severely, active granulomatosis with polyangiitis (75%) and microscopic polyangiitis (24%) were enrolled and treated in an active-comparator, randomised, double-blind, multicentre, 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/m^2) once weekly for 4 weeks. All patients in the cyclophosphamide arm received azathioprine maintenance therapy in during follow-up. Patients in both arms received 1,000 mg of pulse intravenous 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 non-inferiority of rituximab to cyclophosphamide for complete remission (CR) at 6 months (Table 12).

Efficacy was observed both for patients with newly diagnosed disease and for patients with relapsing disease (Table 13).

Table 12 Percentage of patients who achieved complete remission at 6 months (intent-to-treat population*)

	Rituximab (n=99)	Cyclophosphamide (n=98)	Treatment difference (rituximab-cyclophosphamide)
Rate	63.6%	53.1%	10.6% 95.1%[b] CI (-3.2%, 24.3%)[a]

CI = confidence interval
* Worst case imputation
a Non-inferiority was demonstrated since the lower bound (− 3.2%) was higher than the pre-determined non-inferiority margin (− 20%).
b The 95.1% confidence level reflects an additional 0.001 alpha to account for an interim efficacy analysis.

Table 13 Complete remission at 6-months by disease status

	Rituximab	Cyclophosphamide	Difference (CI 95%)
All patients	n=99	n=98	
Newly diagnosed	n=48	n=48	
Relapsing	n=51	n=50	
Complete remission			
All patients	63.6%	53.1%	10.6% (-3.2, 24.3)
Newly diagnosed	60.4%	64.6%	-4.2% (-23.6, 15.3)
Relapsing	66.7%	42.0%	24.7% (5.8, 43.6)

Worst case imputation is applied for patients with missing data

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.

Retreatment with rituximab

Based upon investigator judgment, 15 patients received a second course of rituximab therapy for treatment of relapse of disease activity which occurred between 6 and 18 months after the first course of rituximab. The limited data from the present trial preclude any conclusions regarding the efficacy of subsequent courses of rituximab in patients with granulomatosis with polyangiitis and microscopic polyangiitis.

Continued immunosuppressive therapy may be especially appropriate in patients at risk for relapses (i.e. with history of earlier relapses and granulomatosis with polyangiitis, or patients with reconstitution of B-lymphocytes in addition to PR3-ANCA at monitoring). When remission with rituximab has been achieved, continued immunosuppressive therapy may be considered to prevent relapse. The efficacy and safety of rituximab in maintenance therapy has not been established.

Laboratory evaluations

A total of 23/99 (23%) rituximab-treated patients in the trial tested positive for HACA by 18 months. None of the 99 rituximab-treated patients were HACA positive at screening. The clinical relevance of HACA formation in rituximab-treated patients is unclear.

Comparability of RIXIMYO® with the reference medicine

Demonstration of biosimilarity

RIXIMYO® is a rituximab biosimilar. In studies comparing the pharmaceutical quality and the biological activity, as well as in nonclinical and clinical comparative studies it was demonstrated that RIXIMYO® matches the reference medicine in terms of quality, safety, efficacy and immunogenicity. The level of comparability of RIXIMYO® with the reference medicine that has been shown justifies the use of RIXIMYO® in all indications of the reference medicine.

Comparative clinical trials with RIXIMYO®

PK

A comparable PK profile of RIXIMYO® and the rituximab reference product was demonstrated in a randomised, double-blind trial on patients with active rheumatoid arthritis and supported by a randomised, double-blind trial on treatment-naive patients with follicular lymphoma.

Efficacy, safety, and immunogenicity

Follicular non-Hodgkin's lymphoma

The clinical efficacy of RIXIMYO® compared to the rituximab reference product was investigated in a randomised, double-blind trial in 629 treatment-naive patients with stage III-IV follicular B-cell NHL. In the combination phase of this trial, the patients received 8 cycles of RIXIMYO® or the rituximab reference product (375 mg per m^2 body surface) combined with a CVP chemotherapy. Both treatment groups were balanced with respect to baseline characteristics and disease status. In the subsequent maintenance phase, patients who had responded to treatment (CR or PR) received monotherapy with RIXIMYO® or the rituximab reference product (375 mg per m^2 body surface) over a period of 2 years.

The equivalence of RIXIMYO® and the rituximab reference product was demonstrated on the basis of the primary endpoint - Overall Response Rate at the end of the combination phase.

Rheumatoid arthritis

The clinical efficacy and safety of RIXIMYO® compared to the rituximab reference product were investigated as a secondary endpoint in a randomised, double-blind trial in 173 patients with active rheumatoid arthritis. In this trial, the patients received an i.v. infusion of 1000 mg of either RIXIMYO® or the rituximab reference product at intervals of 15 days, which in each case was given following the infusion of 100 mg methylprednisolone. All patients received simultaneous oral treatment with methotrexate (10−25 mg/week) at a stable dose. The treatment groups were balanced with respect to baseline characteristics and disease status. The primary endpoint of this trial was the pharmacokinetic equivalence of RIXIMYO® and the rituximab reference product. The main endpoint for efficacy was the change in disease activity as assessed by DAS28(CRP) in Week 24 compared to the baseline value. The patients were followed up for a maximum of 1.5 years after enrolment into the trial.

The overall frequencies of common adverse events and serious adverse events were comparable between both treatment groups in follicular non-Hodgkin’s lymphoma (Combination and Maintenance phases) and in rheumatoid arthritis. The safety profiles including immunogenicity of RIXIMYO® in the pivotal populations are consistent with the known safety profile of the reference medicine reported in clinical trials and post-marketing surveillance.

No safety risks were detected in patients who switched from the reference medicine to RIXIMYO®.

In summary, the clinical program for RIXIMYO® confirms a comparable therapeutic efficacy, and comparable safety and immunogenicity profile of RIXIMYO® and rituximab reference product and thus supports biosimilarity.

5.2 Pharmacokinetic properties

Non-Hodgkin's lymphoma

Based on a population pharmacokinetic analysis in 298 NHL patients who received single or multiple infusions of rituximab as a single agent or in combination with CHOP therapy (applied rituximab doses ranged from 100 to 500 mg/m^2), the typical population estimates of nonspecific clearance (CL_1), specific clearance (CL_2) likely contributed by B cells or tumour burden, and central compartment volume of distribution (V_1) were 0.14 L/day, 0.59 L/day, and 2.7 L, respectively. The estimated median terminal elimination half-life of rituximab was 22 days (range, 6.1 to 52 days). Baseline CD19-positive cell counts and size of measurable tumour lesions contributed to some of the variability in CL_2 of rituximab in data from 161 patients given 375 mg/m^2 as an intravenous infusion for 4 weekly doses. Patients with higher CD19-positive cell counts or tumour lesions had a higher CL_2. However, a large component of inter-individual variability remained for CL_2 after correction for CD19-positive cell counts and tumour lesion size. V_1 varied by body surface area (BSA) and CHOP therapy. This variability in V1 (27.1% and 19.0%) contributed by the range in BSA (1.53 to 2.32 m^2) and concurrent CHOP therapy, respectively, were relatively small. Age, gender and WHO performance status had no effect on the pharmacokinetics of rituximab. This analysis suggests that dose adjustment of rituximab with any of the tested covariates is not expected to result in a meaningful reduction in its pharmacokinetic variability.

Rituximab, administered as an intravenous infusion at a dose of 375 mg/m^2 at weekly intervals for 4 doses to 203 patients with NHL naive to rituximab, yielded a mean C_{max} following the fourth infusion of 486 µg/mL (range, 77.5 to 996.6 µg/mL). Rituximab was detectable in the serum of patients 3 to 6 months after completion of last treatment.

Upon administration of rituximab at a dose of 375 mg/m^2 as an intravenous infusion at weekly intervals for 8 doses to 37 patients with NHL, the mean C_{max} increased with each successive infusion, spanning from a mean of 243 µg/mL (range, 16 - 582 µg/mL) after the first infusion to 550 µg/mL (range, 171-1,177 µg/mL) after the eighth infusion.

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

Chronic lymphocytic leukaemia

Rituximab was administered as an intravenous infusion at a first-cycle dose of 375 mg/m^2 increased to 500 mg/m^2 each cycle for 5 doses in combination with fludarabine and cyclophosphamide in CLL patients. The mean C_{max} (n=15) was 408 µg/mL (range, 97 – 764 µg/mL) after the fifth 500 mg/m^2 infusion and the mean terminal half-life was 32 days (range, 14 – 62 days).

Rheumatoid arthritis

Following two intravenous infusions of rituximab at a dose of 1,000 mg, two weeks apart, the mean terminal half-life was 20.8 days (range, 8.58 to 35.9 days), mean systemic clearance was 0.23 l/day (range, 0.091 to 0.67 l/day), and mean steady-state distribution volume was 4.6 l (range, 1.7 to 7.51 l). Population pharmacokinetic analysis of the same data gave similar mean values for systemic clearance and half-life, 0.26 l/day and 20.4 days, respectively. Population pharmacokinetic analysis revealed that BSA and gender were the most significant covariates to explain inter-individual variability in pharmacokinetic parameters. After adjusting for BSA, male subjects had a larger volume of distribution and a faster clearance than female subjects. The gender-related pharmacokinetic differences are not considered to be clinically relevant and dose adjustment is not required. No pharmacokinetic data are available in patients with hepatic or renal impairment.

The pharmacokinetics of rituximab were assessed following two intravenous doses of 500 mg and 1,000 mg on days 1 and 15 in four studies. In all these studies, rituximab pharmacokinetics were dose proportional over the limited dose range studied. Mean C_{max} for serum rituximab following first infusion ranged from 157 to 171 µg/mL for 2 x 500 mg dose and ranged from 298 to 341 µg/mL for 2 x 1,000 mg dose. Following second infusion, mean C_{max} ranged from 183 to 198 µg/mL for the 2 x 500 mg dose and ranged from 355 to 404 µg/mL for the 2 x 1,000 mg dose. Mean terminal elimination half-life

ranged from 15 to 16 days for the 2 x 500 mg dose group and 17 to 21 days for the 2 x 1,000 mg dose group. Mean C_{max} was 16 to 19% higher following second infusion compared to the first infusion for both doses.

The pharmacokinetics of rituximab were assessed following two intravenous doses of 500 mg and 1,000 mg upon re-treatment in the second course. Mean C_{max} for serum rituximab following first infusion was 170 to 175 µg/mL for 2 x 500 mg dose and 317 to 370 µg/mL for 2 x 1,000 mg dose. C_{max} following second infusion, was 207 µg/mL for the 2 x 500 mg dose and ranged from 377 to 386 µg/mL for the 2 x 1,000 mg dose. Mean terminal elimination half-life after the second infusion, following the second course, was 19 days for 2 x 500 mg dose and ranged from 21 to 22 days for the 2 x 1,000 mg dose. PK parameters for rituximab were comparable over the two treatment courses.

The pharmacokinetic (PK) parameters in the anti-TNF inadequate responder population, following the same dose regimen (2 x 1,000 mg, intravenous, 2 weeks apart), were similar with a mean maximum serum concentration of 369 µg/mL and a mean terminal half-life of 19.2 days.

Granulomatosis with polyangiitis and microscopic polyangiitis

Based on the population pharmacokinetic analysis of data in 97 patients with granulomatosis with polyangiitis and microscopic polyangiitis who received 375 mg/m^2 rituximab once weekly for four doses, the estimated median terminal elimination half-life was 23 days (range, 9 – 49 days). Rituximab mean clearance and volume of distribution were 0.313 l/day (range, 0.116 – 0.726 l/day) and 4.50 l (range 2.25 – 7.39 l) respectively. The PK parameters of rituximab in these patients appear similar to what has been observed in rheumatoid arthritis patients.

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
Hydrochloric acid
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial
3 years.

Diluted solution
The prepared infusion solution of RIXIMYO® is physically and chemically stable for 24 hours at 2°C - 8°C and subsequently 12 hours at room temperature (≤ 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. RIXIMYO® vials may be stored below 30ºC for a single period of up to 7 days.

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..

6.6 Special precautions for disposal and other handling

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

Aseptically withdraw the necessary amount of RIXIMYO®, 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. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Sandoz New Zealand Limited
12 Madden Street
Auckland 1010
New Zealand

Telephone: 0800 726 369

9. DATE OF FIRST APPROVAL

12 October 2018

10. DATE OF REVISION OF THE TEXT

24 September 2024

Summary table of changes

Section Changed	Summary of new information
4.2	Addition of Alternative Subsequent, Faster, Infusion Schedule for adult NHL and CLL patients Minor editorial changes
4.8	Update to adverse reaction reporting URL