

**ANNEX I**  
**SUMMARY OF PRODUCT CHARACTERISTICS**

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## 1. NAME OF THE MEDICINAL PRODUCT

Rixathon 100 mg concentrate for solution for infusion

Rixathon 500 mg concentrate for solution for infusion

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

### Rixathon 100 mg concentrate for solution for infusion

Each 10 mL vial contains 100 mg of rituximab.

### Rixathon 500 mg concentrate for solution for infusion

Each 50 mL vial contains 500 mg of rituximab.

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

### Excipient with known effect

This medicinal product contains 2.3 mmol (52.6 mg) sodium per 10 mL vial.

This medicinal product contains 11.5 mmol (263.2 mg) sodium per 50 mL vial.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear, colourless to slightly yellowish liquid.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Rixathon is indicated in adults for the following indications:

#### Non-Hodgkin's lymphoma (NHL)

Rixathon is indicated for the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy.

Rixathon maintenance therapy is indicated for the treatment of follicular lymphoma patients responding to induction therapy.

Rixathon monotherapy is indicated for treatment of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy.

Rixathon is indicated for the treatment of patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy.

#### Chronic lymphocytic leukaemia (CLL)

Rixathon in combination with chemotherapy is indicated for the treatment of patients with previously untreated and relapsed/refractory chronic lymphocytic leukaemia. Only limited data are available on efficacy and safety for patients previously treated with monoclonal antibodies including rituximab or patients refractory to previous rituximab plus chemotherapy.

See section 5.1 for further information.

#### Rheumatoid arthritis

Rixathon in combination with methotrexate is indicated for the treatment of adult patients with severe active rheumatoid arthritis who have had an inadequate response or intolerance to other disease-modifying anti-rheumatic drugs (DMARD) including one or more tumour necrosis factor (TNF) inhibitor therapies.

Rituximab has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate.

#### Granulomatosis with polyangiitis and microscopic polyangiitis

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

#### Pemphigus vulgaris

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

### **4.2 Posology and method of administration**

Rixathon 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 and prophylactic medications

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

In patients with non-Hodgkin's lymphoma and chronic lymphocytic leukaemia, premedication with glucocorticoids should be considered if Rixathon is not given in combination with glucocorticoid-containing chemotherapy.

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

In patients with rheumatoid arthritis, granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis in disease remission or pemphigus vulgaris, premedication with 100 mg intravenous

methylprednisolone should be completed 30 minutes prior to Rixathon infusions to decrease the incidence and severity of infusion related reactions (IRRs).

In patients with granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis, methylprednisolone given intravenously for 1 to 3 days at a dose of 1,000 mg per day is recommended prior to the first infusion of Rixathon (the last dose of methylprednisolone may be given on the same day as the first infusion of Rixathon). This should be followed by oral prednisone 1 mg/kg/day (not to exceed 80 mg/day, and tapered as rapidly as possible based on clinical need) during and after the 4 week induction course of Rixathon treatment.

*Pneumocystis jirovecii* pneumonia (PCP) prophylaxis is recommended for patients with GPA/MPA or PV during and following Rixathon treatment, as appropriate according to local clinical practice guidelines.

### 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

#### *Follicular non-Hodgkin's lymphoma*

#### Combination therapy

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

Rixathon 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 Rixathon used as a maintenance treatment for patients with previously untreated follicular lymphoma who have responded to induction treatment is: 375 mg/m<sup>2</sup> 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 (12 infusions in total).

- Relapsed/refractory follicular lymphoma

The recommended dose of Rixathon used as a maintenance treatment for patients with relapsed/refractory follicular lymphoma who have responded to induction treatment is: 375 mg/m<sup>2</sup> 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 (8 infusions in total).

#### Monotherapy

- Relapsed/refractory follicular lymphoma

The recommended dose of Rixathon 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<sup>2</sup> body surface area, administered as an intravenous infusion once weekly for four weeks.

For retreatment with Rixathon monotherapy for patients who have responded to previous treatment with rituximab monotherapy for relapsed/refractory follicular lymphoma, the recommended dose is: 375 mg/m<sup>2</sup> 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*

Rixathon should be used in combination with CHOP chemotherapy. The recommended dosage is 375 mg/m<sup>2</sup> 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 rituximab 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 Rixathon are recommended. When Rixathon is given in combination with chemotherapy, standard dose reductions for the chemotherapeutic medicinal products should be applied.

### Chronic lymphocytic leukaemia

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

### Rheumatoid arthritis

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

A course of Rixathon consists of two 1,000 mg intravenous infusions. The recommended dosage of Rixathon 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 Rixathon must be given the patient alert card with each infusion.

#### *Induction of remission*

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

#### *Maintenance treatment*

Following induction of remission with Rixathon, maintenance treatment should be initiated no sooner than 16 weeks after the last rituximab infusion.

Following induction of remission with other standard of care immunosuppressants, Rixathon maintenance treatment should be initiated during the 4 week period that follows disease remission.

Rixathon should be administered as two 500 mg IV infusions separated by two weeks, followed by a 500 mg IV infusion every 6 months thereafter. Patients should receive Rixathon for at least 24 months after achievement of remission (absence of clinical signs and symptoms). For patients who may be at higher risk for relapse, physicians should consider a longer duration of Rixathon maintenance therapy, up to 5 years.

### Pemphigus vulgaris

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

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

#### *Maintenance treatment*

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

#### *Treatment of relapse*

In the event of relapse, patients may receive 1000 mg IV. The healthcare provider should also consider resuming or increasing the patient's glucocorticoid dose based on clinical evaluation.

Subsequent infusions may be administered no sooner than 16 weeks following the previous infusion.

### Special populations

#### *Paediatric population*

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

#### *Elderly*

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

### Method of administration

Rixathon is for intravenous use. The prepared Rixathon 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) (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 Rixathon 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 Rixathon 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, microscopic polyangiitis and pemphigus vulgaris

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

Active, severe infections (see section 4.4).

Patients in a severely immunocompromised state.

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

### **4.4 Special warnings and precautions for use**

#### Traceability

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

#### Progressive multifocal leukoencephalopathy

All patients treated with Rixathon for rheumatoid arthritis, granulomatosis with polyangiitis, microscopic polyangiitis or pemphigus vulgaris must be given the patient alert card with each

infusion. The alert card contains important safety information for patients regarding potential increased risk of infections, including progressive multifocal leukoencephalopathy (PML).

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

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

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

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

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

### Non-Hodgkin's lymphoma and chronic lymphocytic leukaemia

#### Infusion-related reactions

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

This set of reactions which includes syndrome of cytokine release, tumour lysis syndrome and anaphylactic and hypersensitivity reactions are described below.

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

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

Patients with a high tumour burden or with a high number ( $\geq 25 \times 10^9/L$ ) of circulating malignant cells such as patients with CLL, who may be at higher risk of especially severe cytokine release syndrome, should be treated with extreme caution. These patients should be very closely monitored throughout the first infusion. Consideration should be given to the use of a reduced infusion rate for the first infusion in these patients or a split dosing over two days during the first cycle and any subsequent cycles if the lymphocyte count is still  $> 25 \times 10^9/L$ .

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

Anaphylactic and other hypersensitivity reactions have been reported following the intravenous administration of proteins to patients. In contrast to cytokine release syndrome, true hypersensitivity reactions typically occur within minutes after starting infusion. Medicinal products for the treatment of hypersensitivity reactions, e.g. epinephrine (adrenaline), antihistamines and glucocorticoids, should be available for immediate use in the event of an allergic reaction during administration of rituximab. Clinical manifestations of anaphylaxis may appear similar to clinical manifestations of the cytokine release syndrome (described above). Reactions attributed to hypersensitivity have been reported less frequently than those attributed to cytokine release.

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

Since hypotension may occur during rituximab administration, consideration should be given to withholding anti-hypertensive medicinal product 12 hours prior to the Rixathon infusion.

#### Cardiac disorders

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

#### Haematological toxicities

Although rituximab is not myelosuppressive in monotherapy, caution should be exercised when considering treatment of patients with neutrophils  $< 1.5 \times 10^9/L$  and/or platelet counts  $< 75 \times 10^9/L$  as clinical experience in this population is limited. Rituximab has been used in 21 patients who underwent autologous bone marrow transplantation and other risk groups with a presumable reduced bone marrow function without inducing myelotoxicity.

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

#### Infections

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

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

Cases of hepatitis B reactivation have been reported in subjects receiving rituximab including fulminant hepatitis with fatal outcome. The majority of these subjects were also exposed to cytotoxic chemotherapy. Limited information from one study in relapsed/refractory CLL patients suggests that rituximab treatment may also worsen the outcome of primary hepatitis B infections. Hepatitis B virus

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

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

#### Immunisations

The safety of immunisation with live viral vaccines, following rituximab therapy has not been studied for NHL and CLL patients and vaccination with live virus vaccines is not recommended. Patients treated with Rixathon 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 titer). For CLL patients similar results are assumable considering similarities between both diseases but that has not been investigated in clinical trials.

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

#### Skin reactions

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

#### Rheumatoid arthritis, granulomatosis with polyangiitis, microscopic polyangiitis, and pemphigus vulgaris

##### 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.

Severe IRRs with fatal outcome have been reported in rheumatoid arthritis patients in the post-marketing setting. In rheumatoid arthritis most infusion-related events reported in clinical trials were mild to moderate in severity. The most common symptoms were allergic reactions like headache, pruritus, throat irritation, flushing, rash, urticaria, hypertension, and pyrexia. In general, the proportion of patients experiencing any infusion reaction was higher following the first infusion than following the second infusion of any treatment course. The incidence of IRR decreased with subsequent courses (see section 4.8). The reactions reported were usually reversible with a reduction in rate, or interruption, of rituximab infusion and administration of an anti-pyretic, an antihistamine, and, occasionally, oxygen, intravenous saline or bronchodilators, and glucocorticoids if required. Closely monitor patients with pre-existing cardiac conditions and those who experienced prior cardiopulmonary adverse reactions. Depending on the severity of the IRR and the required interventions, temporarily or permanently discontinue Rixathon. In most cases, the infusion can be resumed at a 50% reduction in rate (e.g. from 100 mg/h to 50 mg/h) when symptoms have completely resolved.

Medicinal products for the treatment of hypersensitivity reactions, e.g. epinephrine (adrenaline), antihistamines and glucocorticoids, should be available for immediate use in the event of an allergic reaction during administration of Rixathon.

There are no data on the safety of rituximab in patients with moderate heart failure (NYHA class III) or severe, uncontrolled cardiovascular disease. In patients treated with rituximab, the occurrence of pre-existing ischemic cardiac conditions becoming symptomatic, such as angina pectoris, has been observed, as well as atrial fibrillation and flutter. Therefore, in patients with a known cardiac history, and those who experienced prior cardiopulmonary adverse reactions, the risk of cardiovascular complications resulting from infusion reactions should be considered before treatment with Rixathon and patients closely monitored during administration. Since hypotension may occur during rituximab infusion, consideration should be given to withholding anti-hypertensive medicinal products 12 hours prior to the Rixathon infusion.

IRRs for patients with granulomatosis with polyangiitis, microscopic polyangiitis and pemphigus vulgaris were consistent with those seen for rheumatoid arthritis patients in clinical trials (see section 4.8).

#### Cardiac disorders

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

#### Infections

Based on the mechanism of action of rituximab and the knowledge that B cells play an important role in maintaining normal immune response, patients have an increased risk of infection following rituximab therapy (see section 5.1). Serious infections, including fatalities, can occur during therapy with rituximab (see section 4.8). Rixathon should not be administered to patients with an active, severe infection (e.g. tuberculosis, sepsis and opportunistic infections, see section 4.3) or severely immunocompromised patients (e.g. where levels of CD4 or CD8 are very low). 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 Rixathon.

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

Very rare cases of fatal progressive multifocal leukoencephalopathy (PML) have been reported following use of 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 Rixathon. 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 Rixathon, and regularly up to 6-months after cessation of treatment, and upon signs or symptoms of infection (see section 4.8).

#### Skin reactions

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

#### Immunisation

Physicians should review the patient's vaccination status and follow current immunisation guidelines prior to Rixathon therapy. Vaccination should be completed at least 4 weeks prior to first administration of Rixathon.

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

Patients treated with Rixathon 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.

#### Concomitant/sequential use of other DMARDs in rheumatoid arthritis

The concomitant use of Rixathon 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.

#### Sodium

This medicinal product contains 2.3 mmol (or 52.6 mg) sodium per 10 mL vial up to 23.06 mmol (or 530.1 mg) sodium per dose. This medicinal product contains 11.5 mmol (263.2 mg) sodium per 50 mL vial. To be taken into consideration by patients on a controlled sodium diet.

### **4.5 Interaction with other medicinal products and other forms of interaction**

Currently, there are limited data on possible interactions with other medicinal products and 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 (HAMA) or anti-drug antibody (ADA) 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 Rixathon.

##### 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 Rixathon should not be administered to pregnant women unless the possible benefit outweighs the potential risk.

##### Breast-feeding

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

##### Fertility

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

#### **4.7 Effects on ability to drive and use machines**

Rituximab may have a minor influence on the ability to drive and use machines. Dizziness may occur following administration of rituximab (see section 4.8).

## 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 chronic lymphocytic leukaemia is based on data from patients from clinical trials and from post-marketing surveillance. These patients were treated either with rituximab monotherapy (as induction treatment or maintenance treatment following induction treatment) or in combination with chemotherapy.

The most frequently observed adverse 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 (ADRs) 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.)

#### Tabulated list of adverse reactions

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

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

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

System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not known
<b>Infections and infestations</b>	Bacterial infections, viral infections, +bronchitis	Sepsis, +pneumonia, +febrile infection, +herpes zoster, +respiratory tract infection, fungal infections, infections of unknown aetiology, +acute bronchitis, +sinusitis, hepatitis B <sup>1</sup>		Serious viral infection <sup>2</sup> Pneumocystis jirovecii	PML	
<b>Blood and</b>	Neutropenia	Anaemia,	Coagulation		Transient	Late

<b>System Organ Class</b>	<b>Very Common</b>	<b>Common</b>	<b>Uncommon</b>	<b>Rare</b>	<b>Very Rare</b>	<b>Not known</b>
<b>lymphatic system disorders</b>	, leucopenia, +febrile neutropenia, +thrombocytopenia	+pancytopenia, +granulocytopenia	disorders, aplastic anaemia, haemolytic anaemia, lymphadenopathy		increase in serum IgM levels <sup>3</sup>	neutropenia <sup>3</sup>
<b>Immune system disorders</b>	Infusion related reactions <sup>4</sup> , angioedema	Hypersensitivity		Anaphylaxis	Tumour lysis syndrome, cytokine release syndrome <sup>4</sup> , serum sickness	Infusion-related acute reversible thrombocytopenia <sup>4</sup>
<b>Metabolism and nutrition disorders</b>		Hyperglycaemia, weight decrease, peripheral oedema, face oedema, increased LDH, hypocalcaemia				
<b>Psychiatric disorders</b>			Depression, nervousness			
<b>Nervous system disorders</b>		Paraesthesia, hypoaesthesia, agitation, insomnia, vasodilatation, dizziness, anxiety	Dysgeusia		Peripheral neuropathy, facial nerve palsy <sup>5</sup>	Cranial neuropathy, loss of other senses <sup>5</sup>
<b>Eye disorders</b>		Lacrimation disorder, conjunctivitis			Severe vision loss <sup>5</sup>	
<b>Ear and labyrinth disorders</b>		Tinnitus, ear pain				Hearing loss <sup>5</sup>
<b>Cardiac disorders</b>		+Myocardial infarction <sup>4 and 6</sup> , arrhythmia, +atrial fibrillation, tachycardia, +cardiac disorder	+Left ventricular failure, +supraventricular tachycardia, +ventricular tachycardia, +angina, +myocardial ischaemia, bradycardia	Severe cardiac disorders <sup>4 and 6</sup>	Heart failure <sup>4 and 6</sup>	
<b>Vascular disorders</b>		Hypertension, orthostatic hypotension, hypotension			Vasculitis (predominately cutaneous), leukocytoclastic vasculitis	
<b>Respiratory, thoracic and mediastinal disorders</b>		Bronchospasm <sup>4</sup> , respiratory disease, chest pain, dyspnoea, increased cough,	Asthma, bronchiolitis obliterans, lung disorder,	Interstitial lung disease <sup>7</sup>	Respiratory failure <sup>4</sup>	Lung infiltration

System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not known
		rhinitis	hypoxia			
<b>Gastrointestinal disorders</b>	Nausea	Vomiting, diarrhoea, abdominal pain, dysphagia, stomatitis, constipation, dyspepsia, anorexia, throat irritation	Abdominal enlargement		Gastro-intestinal perforation <sup>7</sup>	
<b>Skin and subcutaneous tissue disorders</b>	Pruritis, rash, +alopecia	Urticaria, sweating, night sweats, +skin disorder			Severe bullous skin reactions, Stevens-Johnson Syndrome toxic epidermal necrolysis (Lyell's Syndrome) <sup>7,</sup>	
<b>Musculoskeletal and connective tissue disorders</b>		Hypertonia, myalgia, arthralgia, back pain, neck pain, pain				
<b>Renal and urinary disorders</b>					Renal failure <sup>4</sup>	
<b>General disorders and administration site conditions</b>	Fever, chills, asthenia, headache	Tumour pain, flushing, malaise, cold syndrome, +fatigue, +shivering, +multi-organ failure <sup>4</sup>	Infusion site pain			
<b>Investigations</b>	Decreased IgG levels					
<p>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 (<math>\geq</math> grade 3 NCI common toxicity criteria) reactions. Only the highest frequency observed in the trials is reported</p> <p><sup>1</sup> includes reactivation and primary infections; frequency based on R-FC regimen in relapsed/refractory CLL</p> <p><sup>2</sup> see also section infection below</p> <p><sup>3</sup> see also section haematologic adverse reactions below</p> <p><sup>4</sup> see also section infusion related reactions below. Rarely fatal cases reported</p> <p><sup>5</sup> signs and symptoms of cranial neuropathy. Occurred at various times up to several months after completion of rituximab therapy</p> <p><sup>6</sup> observed mainly in patients with prior cardiac condition and/or cardiotoxic chemotherapy and were mostly associated with infusion-related reactions</p> <p><sup>7</sup> includes fatal cases</p>						

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

Signs and symptoms suggestive of an infusion-related reaction were reported in more than 50% of patients in clinical trials, and were predominantly seen during the first infusion, usually in the first one to two hours. These symptoms mainly comprised fever, chills and rigors. Other symptoms included flushing, angioedema, bronchospasm, vomiting, nausea, urticaria/rash, fatigue, headache, throat

irritation, rhinitis, pruritus, pain, tachycardia, hypertension, hypotension, dyspnoea, dyspepsia, asthenia and features of tumour lysis syndrome. Severe infusion-related reactions (such as bronchospasm, hypotension) occurred in up to 12% of the cases. Additional reactions reported in some cases were myocardial infarction, atrial fibrillation, pulmonary oedema and acute reversible thrombocytopenia. Exacerbations of pre-existing cardiac conditions such as angina pectoris or congestive heart failure or severe cardiac disorders (heart failure, myocardial infarction, atrial fibrillation), pulmonary oedema, multi-organ failure, tumour lysis syndrome, cytokine release syndrome, renal failure, and respiratory failure were reported at lower or unknown frequencies. The incidence of infusion-related symptoms decreased substantially with subsequent infusions and is < 1% of patients by the eighth cycle of rituximab (containing) treatment.

### Description of selected adverse reactions

#### *Infections*

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

Localised candida infections as well as Herpes zoster were reported at a higher incidence in the rituximab-containing arm of randomised studies. Severe infections were reported in about 4% of patients treated with rituximab monotherapy. Higher frequencies of infections overall, including grade 3 or 4 infections, were observed during rituximab maintenance treatment up to 2 years when compared to observation. There was no cumulative toxicity in terms of infections reported over a 2-year treatment period. In addition, other serious viral infections either new, reactivated or exacerbated, some of which were fatal, have been reported with rituximab treatment. The majority of patients had received rituximab in combination with chemotherapy or as part of a haematopoietic stem cell transplant. Examples of these serious viral infections are infections caused by the herpes viruses (Cytomegalovirus, Varicella Zoster Virus and Herpes Simplex Virus), JC virus (progressive multifocal leukoencephalopathy [PML]) and hepatitis C virus. Cases of fatal PML that occurred after disease progression and retreatment have also been reported in clinical trials. Cases of hepatitis B reactivation, have been reported, the majority of which were in patients receiving rituximab in combination with cytotoxic chemotherapy. In patients with relapsed/refractory CLL, the incidence of grade 3/4 hepatitis B infection (reactivation and primary infection) was 2% in R-FC vs. 0% FC. Progression of Kaposi's sarcoma has been observed in rituximab-exposed patients with pre-existing Kaposi's sarcoma. These cases occurred in non-approved indications and the majority of patients were HIV positive.

#### *Haematologic adverse reactions*

In clinical trials with rituximab monotherapy given for 4 weeks, haematological abnormalities occurred in a minority of patients and were usually mild and reversible. Severe (grade 3/4) neutropenia was reported in 4.2%, anaemia in 1.1% and thrombocytopenia in 1.7% of the patients. During rituximab maintenance treatment for up to 2 years, leucopenia (5% vs. 2%, grade 3/4) and neutropenia (10% vs. 4%, grade 3/4) were reported at a higher incidence when compared to observation. The incidence of thrombocytopenia was low (< 1%, grade 3/4) and was not different between treatment arms. During the treatment course in studies with rituximab in combination with chemotherapy, grade 3/4 leucopenia (R-CHOP 88% vs. CHOP 79%, R-FC 23% vs. FC 12%), neutropenia (R-CVP 24% vs. CVP 14%; R-CHOP 97% vs. CHOP 88%, R-FC 30% vs. FC 19% in previously untreated CLL), pancytopenia (R-FC 3% vs. FC 1% in previously untreated CLL) were usually reported with higher frequencies when compared to chemotherapy alone. However, the higher incidence of neutropenia in patients treated with rituximab and chemotherapy was not associated with a higher incidence of infections and infestations compared to patients treated with chemotherapy alone. Studies in previously untreated and relapsed/refractory CLL have established that in up to 25% of patients treated with R-FC neutropenia was prolonged (defined as neutrophil count remaining below  $1 \times 10^9/L$  between day 24 and 42 after the last dose) or occurred with a late onset (defined as neutrophil count below  $1 \times 10^9/L$  later than 42 days after last dose in patients with no previous prolonged neutropenia or who recovered prior to day 42) following treatment with rituximab plus FC. There were no differences reported for the incidence of anaemia. Some cases of late neutropenia occurring more than four weeks after the last infusion of rituximab were reported. In the CLL first-line study, Binet stage C patients experienced more adverse events in the R-FC arm compared to the FC arm (R-FC 83% vs. FC

71%). In the relapsed/refractory CLL study grade 3/4 thrombocytopenia was reported in 11% of patients in the R-FC group compared to 9% of patients in the FC group.

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

#### *Cardiovascular adverse reactions*

Cardiovascular reactions during clinical trials with rituximab monotherapy were reported in 18.8% of patients with the most frequently reported events being hypotension and hypertension. Cases of grade 3 or 4 arrhythmia (including ventricular and supraventricular tachycardia) and angina pectoris during infusion were reported. During maintenance treatment, the incidence of grade 3/4 cardiac disorders was comparable between patients treated with rituximab and observation. Cardiac events were reported as serious adverse events (including atrial fibrillation, myocardial infarction, left ventricular failure, myocardial ischaemia) in 3% of patients treated with rituximab compared to < 1% on observation. In studies evaluating rituximab in combination with chemotherapy, the incidence of grade 3 and 4 cardiac arrhythmias, predominantly supraventricular arrhythmias such as tachycardia and atrial flutter/fibrillation, was higher in the R-CHOP group (14 patients, 6.9%) as compared to the CHOP group (3 patients, 1.5%). All of these arrhythmias either occurred in the context of a rituximab infusion or were associated with predisposing conditions such as fever, infection, acute myocardial infarction or pre-existing respiratory and cardiovascular disease. No difference between the R-CHOP and CHOP group was observed in the incidence of other grade 3 and 4 cardiac events including heart failure, myocardial disease and manifestations of coronary artery disease. In CLL, the overall incidence of grade 3 or 4 cardiac disorders was low both in the first-line study (4% R-FC, 3% FC) and in the relapsed/refractory study (4% R-FC, 4% FC).

#### *Respiratory system*

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

#### *Neurologic disorders*

During the treatment period (induction treatment phase comprising of R-CHOP for at most eight cycles), four patients (2%) treated with R-CHOP, all with cardiovascular risk factors, experienced thromboembolic cerebrovascular accidents during the first treatment cycle. There was no difference between the treatment groups in the incidence of other thromboembolic events. In contrast, three patients (1.5%) had cerebrovascular events in the CHOP group, all of which occurred during the follow-up period. In CLL, the overall incidence of grade 3 or 4 nervous system disorders was low both in the first-line study (4% R-FC, 4% FC) and in the relapsed/refractory study (3% R-FC, 3% FC).

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

#### *Gastrointestinal disorders*

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

#### *IgG levels*

In the clinical trial evaluating rituximab maintenance treatment 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 ( $\geq 65$ 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 ( $\geq 65$ 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 3,100 patients received at least one treatment course and were followed for periods ranging from 6 months to over 5 years; approximately 2,400 patients received two or more courses of treatment with over 1,000 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 1,000 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.

##### Tabulated list of adverse reactions

Adverse reactions are listed in Table 2. Frequencies are defined as very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  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 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.

**Table 2 Summary of ADRs reported in clinical trials or during postmarketing surveillance occurring in patients with rheumatoid arthritis receiving rituximab**

<b>System Organ Class</b>	<b>Very Common</b>	<b>Common</b>	<b>Uncommon</b>	<b>Rare</b>	<b>Very rare</b>
<b>Infections and infestations</b>	Upper respiratory tract infection, urinary tract infections	Bronchitis, sinusitis, gastroenteritis, tinea pedis			PML, reactivation of hepatitis B
<b>Blood and lymphatic system disorders</b>		Neutropenia <sup>1</sup>		Late neutropenia <sup>2</sup>	Serum ickness-like reaction
<b>Immune system disorders</b>	Infusion-related reactions <sup>3</sup> (hypertension, nausea, rash, pyrexia, pruritus, urticaria, throat irritation, hot flush, hypotension, rhinitis, rigors, tachycardia, fatigue, oropharyngeal pain, peripheral oedema, erythma)		Infusion-related reactions <sup>3</sup> (generalised oedema, bronchospasm, wheezing, laryngeal oedema, angioneurotic oedema, generalised pruritus, anaphylaxis, anaphylactoid reaction)		
<b>General disorders and administration site conditions</b>					
<b>Metabolism and nutrition disorders</b>		Hypercholesterolemia			
<b>Psychiatric disorders</b>		Depression, anxiety			
<b>Nervous system disorders</b>	Headache	Paraesthesia, migraine, dizziness, sciatica			
<b>Cardiac disorders</b>				Angina pectoris, atrial fibrillation, heart failure, myocardial infarction	Atrial flutter

<b>System Organ Class</b>	<b>Very Common</b>	<b>Common</b>	<b>Uncommon</b>	<b>Rare</b>	<b>Very rare</b>
<b>Gastrointestinal disorders</b>		Dyspepsia, diarrhoea, gastro-oesophageal reflux, mouth ulceration, upper abdominal pain			
<b>Skin and subcutaneous tissue disorders</b>		Alopecia			Toxic Epidermal Necrolysis (Lyell's syndrome), Stevens-Johnson syndrome <sup>5</sup>
<b>Musculoskeletal and connective tissue disorders</b>		Arthralgia / musculoskeletal pain, osteoarthritis, bursitis			
<b>Investigations</b>	Decreased IgM levels <sup>4</sup>	Decreased IgG levels <sup>4</sup>			
<p><sup>1</sup> Frequency category derived from laboratory values collected as part of routine laboratory monitoring in clinical trials</p> <p><sup>2</sup> Frequency category derived from post-marketing data.</p> <p><sup>3</sup> 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.</p> <p><sup>4</sup> Includes observations collected as part of routine laboratory monitoring.</p> <p><sup>5</sup> Includes fatal cases</p>					

#### *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.

#### *Description of selected adverse reactions*

##### *Infusion-related reactions*

The most frequent ADRs following receipt of rituximab in clinical studies were IRRs (refer to Table 2). Among the 3189 patients treated with rituximab, 1,135 (36%) experienced at least one IRR with 733/3,189 (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% (17/3,189) 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 sections 4.2 and 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.

#### *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 intravenous 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% (13/1,382) 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

##### *Induction of remission*

Ninety-nine patients were treated for induction of remission of GPA and MPA in a clinical trial with rituximab (375 mg/m<sup>2</sup>, once weekly for 4 weeks) and glucocorticoids (see section 5.1).

The ADRs listed in Table 3 were all adverse events which occurred at an incidence of  $\geq 5\%$  in the rituximab group and at a higher frequency than the comparator group.

**Table 3 Adverse drug reactions occurring at 6-months in  $\geq 5\%$  of patients receiving rituximab for induction of remission of GPA and MPA, and at a higher frequency than the comparator group.**

<b>Body System</b>	<b>Rituximab</b>
<b>Adverse event</b>	<b>(n=99)</b>
<b>Infections and infestations</b>	
Urinary tract infection	7%
Bronchitis	5%
Herpes zoster	5%
Nasopharyngitis	5%
<b>Blood and lymphatic system disorders</b>	
Thrombocytopenia	7%
<b>Immune system disorders</b>	
Cytokine release syndrome	5%
<b>Metabolism and nutrition disorders</b>	
Hyperkalaemia	5%
<b>Psychiatric disorders</b>	
Insomnia	14%
<b>Nervous system disorders</b>	
Dizziness	10%
Tremor	10%
<b>Vascular disorders</b>	
Hypertension	12%
Flushing	5%
<b>Respiratory, thoracic and mediastinal disorders</b>	
Cough	12%
Dyspnoea	11%
Epistaxis	11%
Nasal congestion	6%
<b>Gastrointestinal disorders</b>	
Diarrhoea	18%
Dyspepsia	6%
Constipation	5%
<b>Skin and subcutaneous tissue disorders</b>	
Acne	7%
<b>Musculoskeletal and connective tissue disorders</b>	
Muscle spasms	18%
Arthralgia	15%
Back pain	10%
Muscle weakness	5%
Musculoskeletal pain	5%
Pain in extremities	5%

<b>Body System</b>	<b>Rituximab</b>
<b>Adverse event</b>	<b>(n=99)</b>
<b>General disorders and administration site conditions</b>	
Peripheral oedema	16%
<b>Investigations</b>	
Decreased haemoglobin	6%

#### *Maintenance treatment*

In a further clinical study, a total of 57 severe, active GPA and MPA patients in disease remission were treated with rituximab for the maintenance of remission (see section 5.1).

**Table 4 Adverse drug reactions occurring in  $\geq 5\%$  of patients receiving rituximab for maintenance treatment of GPA and MPA, and at a higher frequency than the comparator group**

<b>System Organ Class</b>	<b>Rituximab</b>
<b>Adverse drug reaction<sup>1</sup></b>	<b>(n=57)</b>
<b>Infections and infestations</b>	
Bronchitis	14%
Rhinitis	5%
<b>General disorders and administration site conditions</b>	
Pyrexia	9%
Influenza-like illness	5%
Oedema peripheral	5%
<b>Gastrointestinal disorders</b>	
Diarrhoea	7%
<b>Respiratory, thoracic and mediastinal disorders</b>	
Dyspnoea	9%
<b>Injury, poisoning and procedural complications</b>	
Infusion-related reactions <sup>2</sup>	12%
<sup>1</sup> Events were considered ADRs only after thorough assessment and where a causal relationship between the medicinal product and the adverse event was at least a reasonable possibility.	
<sup>2</sup> Details on infusion related reactions are provided in the description of selected adverse drug reactions section.	

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

The most commonly reported events considered as ADRs were infusion-related reactions and infections.

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

#### Description of selected adverse reactions

##### *Infusion-related reactions*

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

In the maintenance therapy clinical trial, 7/57 (12%) patients in the rituximab arm experienced at least one infusion-related reaction. The incidence of IRR symptoms was highest during or after the first infusion (9%) and decreased with subsequent infusions (<4%). All IRR symptoms were mild or moderate and most of them were reported from the SOCs Respiratory, Thoracic and Mediastinal Disorders and Skin and Subcutaneous Tissue disorders.

### *Infections*

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

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

### *Malignancies*

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

### *Cardiovascular adverse reactions*

In the clinical trial on induction of remission, cardiac events occurred at a rate of approximately 273 per 100 patient years (95% CI 149 - 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 postmarketing setting.

### *Hypogammaglobulinaemia*

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

In the induction of remission clinical trial, at 6 months, in the rituximab group, 27%, 58% and 51% of patients with normal immunoglobulin levels at baseline, had low IgA, IgG and IgM levels, respectively compared to 25%, 50% and 46% in the cyclophosphamide group.

In the maintenance therapy clinical trial, no clinically meaningful differences between the two treatment arms or decreases in total immunoglobulin, IgG, IgM or IgA levels were observed throughout the trial.

### *Neutropenia*

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

In the maintenance therapy clinical trial, the incidence of all-grade neutropenia was 0% for rituximab-treated patients vs 5% for azathioprine treated patients.

### *Skin and subcutaneous tissue disorders*

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

### Experience from pemphigus vulgaris

#### Summary of the safety profile

The safety profile of rituximab in combination with short-term, low-dose glucocorticoids in the treatment of patients with pemphigus vulgaris was studied in a Phase 3, randomised, controlled, multicenter, open-label study in pemphigus patients that included 38 pemphigus vulgaris (PV) patients randomised to the rituximab group. Patients randomised to the rituximab group received an initial 1000 mg IV on Study Day 1 and a second 1000 mg IV on Study Day 15. Maintenance doses of 500 mg IV were administered at months 12 and 18. Patients could receive 1000 mg IV at the time of relapse (see section 5.1).

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

#### Tabulated list of adverse reactions

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

**Table 5 Adverse drugs reactions for rituximab-treated pemphigus vulgaris patients in the clinical study up to month 24**

<b>System Organ Class</b> Adverse drug reaction	<b>rituximab + low-dose prednisone</b> <b>(n = 38)</b>
<b>Injury, Poisoning and Procedural Complications</b>	
Infusion-related reactions*	58%

<b>Skin and Subcutaneous Tissue Disorders</b>	
Alopecia	13%
Pruritus	5%
Urticaria	5%
Skin disorder	5%
<b>Psychiatric Disorders</b>	
Persistent depressive disorder	13%
Major depression	5%
Irritability	5%
<b>Infections and Infestations</b>	
Herpes virus infection	8%
Herpes zoster	5%
Oral herpes	5%
Conjunctivitis	5%
<b>General Disorders and Administration Site Conditions</b>	
Fatigue	8%
Pyrexia	5%
<b>Nervous System Disorders</b>	
Headache	5%
Dizziness	5%
<b>Gastrointestinal Disorders</b>	
Abdominal pain upper	5%
<b>Cardiac Disorders</b>	
Tachycardia	5%
<b>Musculoskeletal and Connective Tissue Disorders</b>	
Musculoskeletal pain	5%
<b>Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)</b>	
Skin papilloma	5%
* Infusion-related reactions included symptoms collected on the next scheduled visit after each infusion, and adverse events occurring on the day of or one day after the infusion. The most common infusion-related reaction symptoms/Preferred Terms included headaches, chills, high blood pressure, nausea, asthenia and pain.	

### Description of selected adverse reactions

#### *Infusion-related reactions*

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

#### *Infections*

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

## Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

### **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 5,000 mg (2,250 mg/m<sup>2</sup>), tested in a dose escalation study in patients with chronic lymphocytic leukaemia. No additional safety signals were identified.

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

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

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

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

Rixathon is a biosimilar medicinal product. Detailed information is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

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/ $\mu$ L after two weekly infusions of rituximab 375 mg/m<sup>2</sup>, 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/ $\mu$ L 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<sup>2</sup> 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<sub>95%</sub> 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<sup>2</sup> 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  $\geq$  10 cm in diameter), low grade or follicular B cell NHL received 375 mg/m<sup>2</sup> of rituximab as intravenous infusion weekly for four doses. The ORR was 36% (CI<sub>95%</sub> 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<sup>2</sup> 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<sub>95%</sub> 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<sup>2</sup>,

vincristine 1.4 mg/m<sup>2</sup> up to a maximum of 2 mg on day 1, and prednisolone 40 mg/m<sup>2</sup>/day on days 1 - 5 every 3 weeks for 8 cycles or rituximab 375 mg/m<sup>2</sup> 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- $\alpha$ ) 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 6.

**Table 6 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, %
<b>M39021</b>	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 $p=0.029$
<b>GLSG'00</b>	CHOP, 205 R-CHOP, 223	18	90 96	17 20	Median TTF: 2.6 years Not reached $p < 0.001$	18-months 90 95 $p=0.016$
<b>OSHO-39</b>	MCP, 96 R-MCP, 105	47	75 92	25 50	Median PFS: 28.8 Not reached $p < 0.0001$	48-months 74 87 $p=0.0096$
<b>FL2000</b>	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<sup>2</sup> body surface area given every 2 months until disease progression or for a maximum period of two years.

The pre-specified primary analysis was conducted at a median observation time of 25 months from randomization, maintenance therapy with rituximab resulted in a clinically relevant and statistically significant improvement in the primary endpoint of investigator assessed progression-free survival (PFS) as compared to observation in patients with previously untreated follicular lymphoma (Table 7).

Significant benefit from maintenance treatment with rituximab was also seen for the secondary endpoints event-free survival (EFS), time to next anti-lymphoma treatment (TNLT) time to next chemotherapy (TNCT) and overall response rate (ORR) in the primary analysis (Table 7).

Data from extended follow up of patients in the study (median follow-up 9 years) confirmed the long-term benefit of rituximab maintenance therapy in terms of PFS, EFS, TNLT, and TNCT (Table 7).

**Table 7 Overview of efficacy results for rituximab maintenance vs. observation at the protocol-defined primary analysis and after 9 years median follow-up (final analysis)**

	Primary analysis (median FU: 25 months)		Final analysis (median FU:9.0 years)	
	Observation N=513	Rituximab N=505	Observation N=513	Rituximab N=505
<b>Primary efficacy</b>				
Progression-free survival (median)	NR	NR	4.06 years	10.49 years
log-rank p value	<0.0001		<0.0001	
hazard ratio (95% CI)	0.50 (0.39, 0.64)		0.61 (0.52, 0.73)	
risk reduction	50%		39%	
<b>Secondary efficacy</b>				
Overall survival (median)	NR	NR	NR	NR
log-rank p value	0.7246		0.7948	
hazard ratio (95% CI)	0.89 (0.45, 1.74)		1.04 (0.77, 1.40)	
risk reduction	11%		-6%	
Event-free survival (median)	38 months	NR	4.04 years	9.25 years
log-rank p value	<0.0001		<0.0001	
hazard ratio (95% CI)	0.54 (0.43, 0.69)		0.64 (0.54, 0.76)	
risk reduction	46%		36%	
TNLT (median)	NR	NR	6.11 years	NR
log-rank p value	0.0003		<0.0001	
hazard ratio (95% CI)	0.61 (0.46, 0.80)		0.66 (0.55, 0.78)	
risk reduction	39%		34%	
TNCT (median)	NR	NR	9.32 years	NR
log-rank p value	0.0011		0.0004	
hazard ratio (95% CI)	0.60 (0.44, 0.82)		0.71 (0.59, 0.86)	
risk reduction	40%		39%	
Overall response rate*	55%	74%	61%	79%
chi-squared test p value	<0.0001		<0.0001	
odds ratio (95% CI)	2.33 (1.73, 3.15)		2.43 (1.84, 3.22)	
Complete response (CR/CRu) rate*	48%	67%	53%	67%
chi-squared test p value	<0.0001		<0.0001	
odds ratio (95% CI)	2.21 (1.65, 2.94)		2.34 (1.80, 3.03)	

\* at end of maintenance/observation; final analysis results based on median follow-up of 73 months.

FU: follow-up; NR: not reached at time of clinical cut off, TNCT: time to next chemotherapy treatment; TNLT: time to next anti lymphoma treatment.

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<sup>2</sup> 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 8).

**Table 8 Induction phase: overview of efficacy results for CHOP vs. R-CHOP (31 months median observation time)**

	CHOP	R-CHOP	p-value	Risk reduction <sup>1)</sup>
<b>Primary efficacy</b>				
ORR <sup>2)</sup>	74%	87%	0.0003	NA
CR <sup>2)</sup>	16%	29%	0.0005	NA
PR <sup>2)</sup>	58%	58%	0.9449	NA

<sup>1)</sup> Estimates were calculated by hazard ratios

<sup>2)</sup> 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 9 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	20.1	38.8	< 0.0001	50%

Efficacy parameter	Kaplan-Meier estimate of median time to event (months)			Risk reduction
	Observation (N=167)	Rituximab (N=167)	Log-rank p value	
Disease-free survival <sup>a</sup>	16.5	53.7	0.0003	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 9). 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<sup>2</sup>, doxorubicin 50 mg/m<sup>2</sup>, vincristine 1.4 mg/m<sup>2</sup> up to a maximum of 2 mg on day 1, and prednisolone 40 mg/m<sup>2</sup>/day on days 1-5) every 3 weeks for eight cycles, or rituximab 375 mg/m<sup>2</sup> 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,  $\beta_2$  microglobulin, LDH, albumin, B symptoms, bulky disease, extranodal sites, bone marrow involvement), the risk ratios for event-free survival and overall survival (R-CHOP compared with CHOP) were less than 0.83 and 0.95

respectively. R-CHOP was associated with improvements in outcome for both high- and low-risk patients according to age adjusted IPI.

### Clinical laboratory findings

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

### Chronic lymphocytic leukaemia

In two open-label randomised trials, a total of 817 previously untreated patients and 552 patients with relapsed/refractory CLL were randomised to receive either FC chemotherapy (fludarabine 25 mg/m<sup>2</sup>, cyclophosphamide 250 mg/m<sup>2</sup>, days 1-3) every 4 weeks for 6 cycles or rituximab in combination with FC (R-FC). Rituximab was administered at a dosage of 375 mg/m<sup>2</sup> during the first cycle one day prior to chemotherapy and at a dosage of 500 mg/m<sup>2</sup> 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 10a and Table 10b) and 552 patients (276 R-FC, 276 FC) for the relapsed/refractory study (Table 11) 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 10a). 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 10b).

**Table 10a 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=408)	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)	72.6%	85.8%	< 0.0001	n.a.
CR rates	16.9%	36.0%	< 0.0001	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 10b 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 11 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 *	27.6	39.6	0.0252	31%
Disease free survival (DFS)**	42.2	39.6	0.8842	-6%
Time to new CLL treatment	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, multicenter 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 12). 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 12 Clinical response outcomes at primary endpoint in Trial 1 (ITT population)**

	Outcome†	Placebo+MTX	Rituximab+MTX (2 x 1,000 mg)
Trial 1		N=201	N=298
	ACR20	36 (18%)	153 (51%)*
	ACR50	11 (5%)	80 (27%)*
	ACR70	3 (1%)	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 12). 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 12).

#### *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 13).

**Table 13 Radiographic outcomes at 1 year (mITT population)**

	Placebo+MTX	Rituximab+MTX 2 x 1,000 mg
<b>Trial 1</b>	(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**
Proportion of patients with no radiographic change	46%	53%, NS
Proportion 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 14).

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 14).

**Table 14 Physical Function and Quality of Life outcomes at week 24 in Trial 1**

Outcome†	Placebo+MTX	Rituximab+MTX (2 x 1,000 mg)
	n=201	n=298
Mean change in HAQ-DI	0.1	-0.4***
% HAQ-DI MCID	20%	51%
Mean change in FACIT-T	-0.5	-9.1***
	n=197	n=294
Mean change in SF-36 PHS	0.9	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  $\geq 0.22$ , 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.

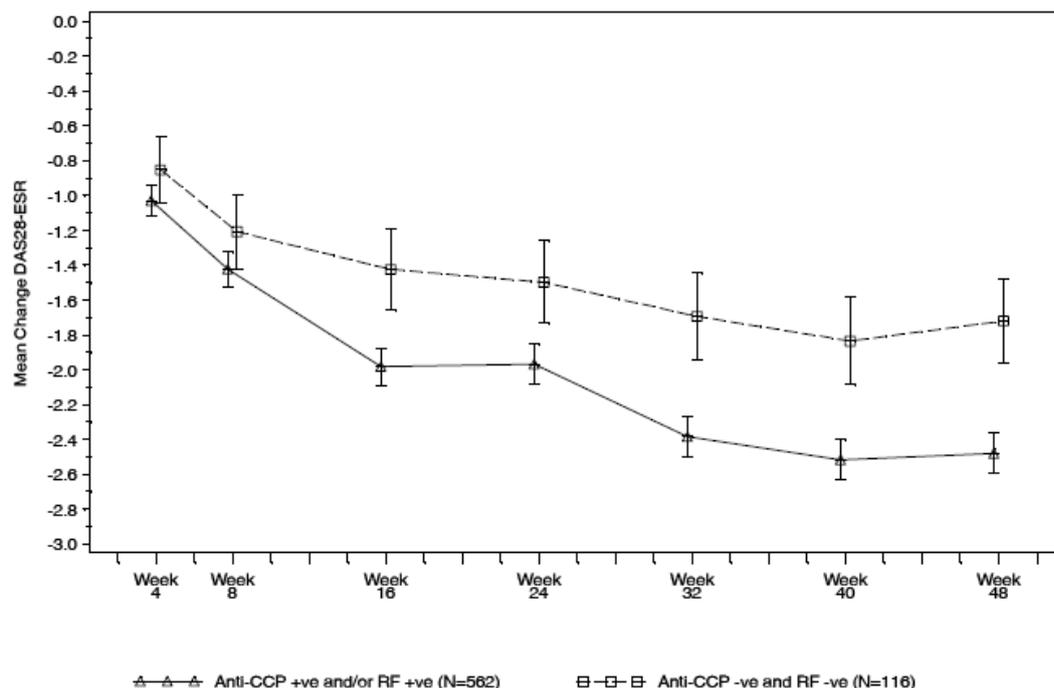
Efficacy outcomes in rituximab treated patients were analysed based on autoantibody status prior to commencing treatment. At week 24, patients who were seropositive to RF and/or anti-CCP at baseline had a significantly increased probability of achieving ACR20 and 50 responses compared to seronegative patients ( $p=0.0312$  and  $p=0.0096$ ) (Table 15). 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 15 Summary of efficacy by baseline autoantibody status**

	Week 24		Week 48	
	Seropositive (n=514)	Seronegative (n=106)	Seropositive (n=506)	Seronegative (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 \*  $p < 0.05$ , \*\*  $p < 0.001$ , \*\*\*  $p < 0.0001$ .

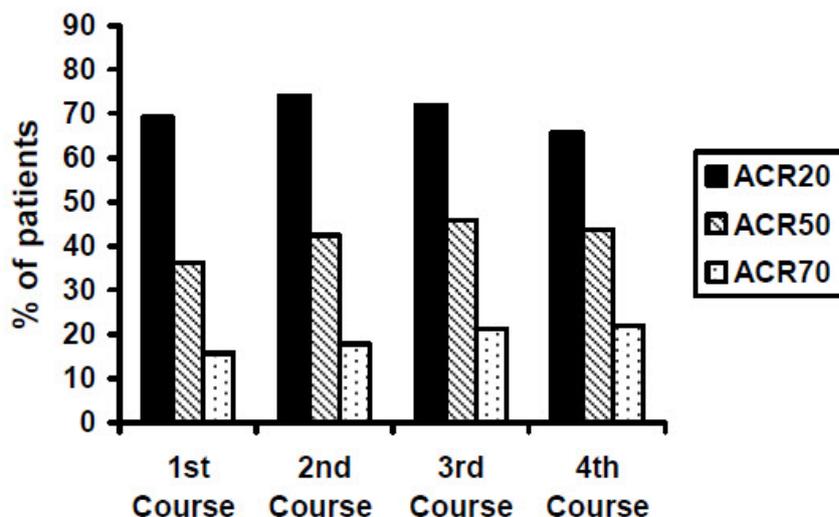
**Figure 1: Change from baseline of DAS28-ESR by baseline autoantibody status**



*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 ADA in clinical studies following therapy with rituximab. The emergence of ADA was not associated with clinical deterioration or with an increased risk of reactions to subsequent infusions in the majority of patients.

The presence of ADA 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

Induction of remission

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, multicenter, non-inferiority trial.

Patients were randomised in a 1:1 ratio to receive either oral cyclophosphamide daily (2 mg/kg/day) for 3-6 months or rituximab (375 mg/m<sup>2</sup>) 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 16).

Efficacy was observed both for patients with newly diagnosed disease and for patients with relapsing disease (Table 17).

**Table 16 Percentage of patients who achieved complete remission at 6 months (intent-to-treat population\*)**

	<b>Rituximab (n=99)</b>	<b>Cyclophosphamide (n=98)</b>	<b>Treatment difference (rituximab-cyclophosphamide)</b>
Rate	63.6%	53.1%	10.6% 95.1% <sup>b</sup> CI (-3.2%, 24.3%) <sup>a</sup>
– CI = confidence interval. – * Worst case imputation <sup>a</sup> Non-inferiority was demonstrated since the lower bound (- 3.2%) was higher than the pre-determined non-inferiority margin (- 20%). <sup>b</sup> The 95.1% confidence level reflects an additional 0.001 alpha to account for an interim efficacy analysis.			

**Table 17 Complete remission at 6-months by disease status**

	<b>Rituximab</b>	<b>Cyclophosphamide</b>	<b>Difference (CI 95%)</b>
<b>All patients</b>	n=99	n=98	
<b>Newly diagnosed</b>	n=48	n=48	
<b>Relapsing</b>	n=51	n=50	
<b>Complete remission</b>			
<b>All patients</b>	63.6%	53.1%	10.6% (-3.2, 24.3)
<b>Newly diagnosed</b>	60.4%	64.6%	-4.2% (-23.6, 15.3)
<b>Relapsing</b>	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.

#### *Laboratory evaluations*

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

#### *Maintenance treatment*

A total of 117 patients (88 with GPA, 24 with MPA, and 5 with renal-limited ANCA-associated vasculitis) in disease remission were randomized to receive azathioprine (59 patients) or rituximab (58 patients) in a prospective, multi-center, controlled, open-label study. Included patients were 21 to 75 years of age and had newly diagnosed or relapsing disease in complete remission after combined treatment with glucocorticoids and pulse cyclophosphamide. The majority of patients were ANCA-positive at diagnosis or during the course of their disease; had histologically confirmed necrotizing small-vessel vasculitis with a clinical phenotype of GPA/MPA, or renal limited ANCA-associated vasculitis; or both.

Remission-induction therapy included IV prednisone, administered as per the investigator's discretion, preceded in some patients by methylprednisolone pulses, and pulse cyclophosphamide until remission was attained after 4 to 6 months. At that time, and within a maximum of 1 month after the last cyclophosphamide pulse, patients were randomly assigned to receive either rituximab (two 500 mg IV infusions separated by two weeks (on Day 1 and Day 15) followed by 500 mg IV every 6 months for 18 months) or azathioprine (administered orally at a dose of 2 mg/kg/day for 12 months, then 1.5 mg/kg/day for 6 months, and finally 1 mg/kg/day for 4 months (treatment discontinuation after these 22 months)). Prednisone treatment was tapered and then kept at a low dose (approximately 5 mg per day) for at least 18 months after randomization. Prednisone dose tapering and the decision to stop prednisone treatment after month 18 were left at the investigator's discretion.

All patients were followed until month 28 (10 or 6 months, respectively, after the last rituximab infusion or azathioprine dose). *Pneumocystis jirovecii* pneumonia prophylaxis was required for all patients with CD4+ T-lymphocyte counts less than 250 per cubic millimeter.

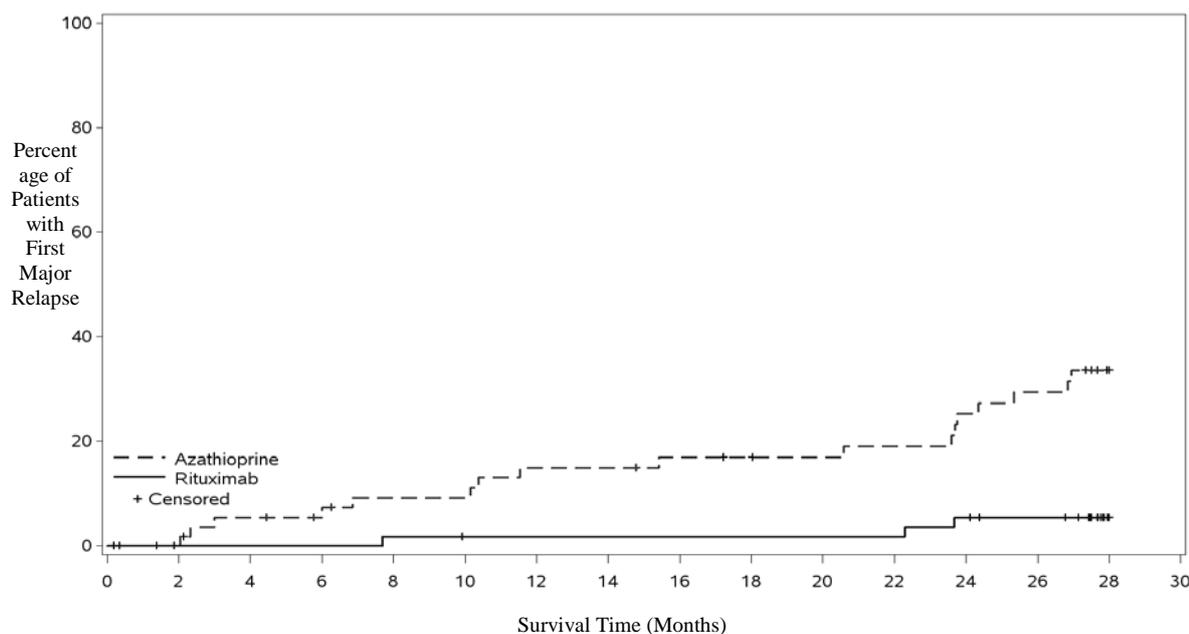
The primary outcome measure was the rate of major relapse at month 28.

### Results

At month 28, major relapse (defined by the reappearance of clinical and/or laboratory signs of vasculitis activity ([BVAS] > 0) that could lead to organ failure or damage or could be life threatening) occurred in 3 patients (5%) in the rituximab group and 17 patients (29%) in the azathioprine group (p=0.0007). Minor relapses (not life threatening and not involving major organ damage) occurred in seven patients in the rituximab group (12%) and eight patients in the azathioprine group (14%).

The cumulative incidence rate curves showed that time to first major relapse was longer in patients with rituximab starting from month 2 and was maintained up to month 28 (Figure 3).

**Figure 3: Cumulative incidence over time of first major relapse**



Number of Subjects with Major Relapse																
Azathioprine	0	0	3	3	5	5	8	8	9	9	9	10	13	15	17	
Rituximab	0	0	0	0	1	1	1	1	1	1	1	1	3	3	3	
Number of subjects at risk																
Azathioprine	59	56	52	50	47	47	44	44	42	41	40	39	36	34	0	
Rituximab	58	56	56	56	55	54	54	54	54	54	54	54	52	50	0	

Note: Patients were censored at month 28 if they had no event.

### Laboratory evaluations

A total of 6/34 (18%) of rituximab treated patients from the maintenance therapy clinical trial developed ADA. There was no apparent negative impact of the presence of ADA on safety or efficacy in the maintenance therapy clinical trial.

### Clinical experience in pemphigus vulgaris

The efficacy and safety of rituximab in combination with short-term, low-dose glucocorticoid (prednisone) therapy were evaluated in newly diagnosed patients with moderate to severe pemphigus (74 pemphigus vulgaris [PV] and 16 pemphigus foliaceus [PF]) in this randomised, open-label, controlled, multicenter study. Patients were between 19 and 79 years of age and had not received prior therapies for pemphigus. In the PV population, 5 (13%) patients in the rituximab group and 3 (8%) patients in the standard prednisone group had moderate disease and 33 (87%) patients in the rituximab group and 33 (92%) patients in the standard-dose prednisone group had severe disease according to disease severity defined by Harman's criteria.

Patients were stratified by baseline disease severity (moderate or severe) and randomised 1:1 to receive either rituximab and low-dose prednisone or standard-dose prednisone. Patients randomised to the rituximab group received an initial intravenous infusion of 1000 mg rituximab on Study Day 1 in combination with 0.5 mg/kg/day oral prednisone tapered off over 3 months if they had moderate disease or 1 mg/kg/day oral prednisone tapered off over 6 months if they had severe disease, and a second intravenous infusion of 1000 mg on Study Day 15. Maintenance infusions of rituximab 500 mg were administered at months 12 and 18. Patients randomised to the standard-dose prednisone group received an initial 1 mg/kg/day oral prednisone tapered off over 12 months if they had moderate disease or 1.5 mg/kg/day oral prednisone tapered off over 18 months if they had severe disease. Patients in the rituximab group who relapsed could receive an additional infusion of rituximab 1000 mg in combination with reintroduced or escalated prednisone dose. Maintenance and relapse infusions were administered no sooner than 16 weeks following the previous infusion.

The primary objective for the study was complete remission (complete epithelialisation and absence of new and/or established lesions) at month 24 without the use of prednisone therapy for two months or more (CROff for  $\geq 2$  months).

**Results**

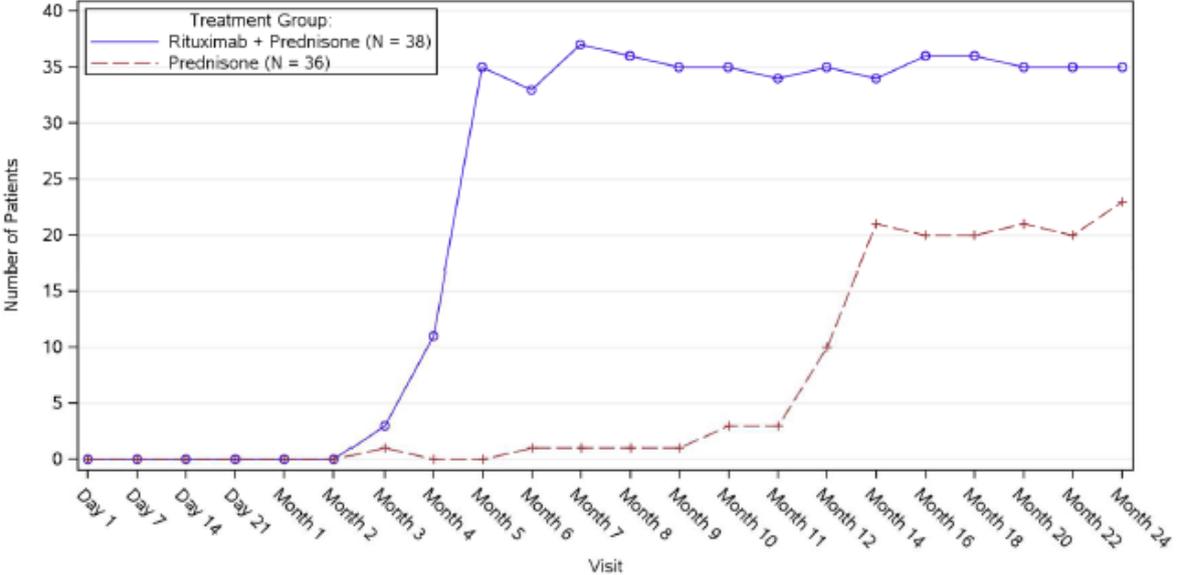
The study showed statistically significant results of rituximab and low-dose prednisone over standard-dose prednisone in achieving CROff  $\geq 2$  months at month 24 in PV patients (see Table 18).

**Table 18 Percentage of PV patients who achieved complete remission off corticosteroid therapy for two months or more at month 24 (Intent-to-Treat Population - PV)**

	Rituximab + Prednisone N=38	Prednisone N=36	p-value <sup>a</sup>	95% CI <sup>b</sup>
Number of responders (response rate [%])	34 (89.5%)	10 (27.8%)	<0.0001	61.7% (38.4, 76.5)
<sup>a</sup> p-value is from Fisher’s exact test with mid-p correction				
<sup>b</sup> 95% confidence interval is corrected Newcombe interval				

The number of rituximab plus low-dose prednisone patients off prednisone therapy or on minimal therapy (prednisone dose of 10 mg or less per day) compared to standard-dose prednisone patients over the 24-month treatment period shows a steroid-sparing effect of rituximab (Figure 4).

**Figure 4: Number of patients who were off or on minimal corticosteroid ( $\leq 10$ mg/day) therapy over time**



### *Post-hoc retrospective laboratory evaluation*

A total of 19/34 (56%) patients with PV, who were treated with rituximab, tested positive for ADA antibodies by 18 months. The clinical relevance of ADA formation in rituximab-treated PV patients is unclear.

## **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<sup>2</sup>), the typical population estimates of nonspecific clearance (CL<sub>1</sub>), specific clearance (CL<sub>2</sub>) likely contributed by B cells or tumour burden, and central compartment volume of distribution (V<sub>1</sub>) 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<sub>2</sub> of rituximab in data from 161 patients given 375 mg/m<sup>2</sup> as an intravenous infusion for 4 weekly doses. Patients with higher CD19-positive cell counts or tumour lesions had a higher CL<sub>2</sub>. However, a large component of inter-individual variability remained for CL<sub>2</sub> after correction for CD19-positive cell counts and tumour lesion size. V<sub>1</sub> varied by body surface area (BSA) and CHOP therapy. This variability in V<sub>1</sub> (27.1% and 19.0%) contributed by the range in BSA (1.53 to 2.32 m<sup>2</sup>) 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<sup>2</sup> at weekly intervals for 4 doses to 203 patients with NHL naive to rituximab, yielded a mean C<sub>max</sub> 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<sup>2</sup> as an intravenous infusion at weekly intervals for 8 doses to 37 patients with NHL, the mean C<sub>max</sub> 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<sup>2</sup> 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<sup>2</sup> increased to 500 mg/m<sup>2</sup> each cycle for 5 doses in combination with fludarabine and cyclophosphamide in CLL patients. The mean C<sub>max</sub> (N=15) was 408 µg/mL (range, 97 – 764 µg/mL) after the fifth 500 mg/m<sup>2</sup> 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  $\mu\text{g/mL}$  for 2 x 500 mg dose and ranged from 298 to 341  $\mu\text{g/mL}$  for 2 x 1,000 mg dose. Following second infusion, mean  $C_{max}$  ranged from 183 to 198  $\mu\text{g/mL}$  for the 2 x 500 mg dose and ranged from 355 to 404  $\mu\text{g/mL}$  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  $\mu\text{g/mL}$  for 2 x 500 mg dose and 317 to 370  $\mu\text{g/mL}$  for 2 x 1,000 mg dose.  $C_{max}$  following second infusion, was 207  $\mu\text{g/mL}$  for the 2 x 500 mg dose and ranged from 377 to 386  $\mu\text{g/mL}$  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 dosage regimen (2 x 1,000 mg, intravenous, 2 weeks apart), were similar with a mean maximum serum concentration of 369  $\mu\text{g/mL}$  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  $\text{mg/m}^2$  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 Rixathon and polyvinyl chloride or polyethylene bags or infusion sets have been observed.

### **6.3 Shelf life**

#### Unopened vial

3 years.

#### Diluted solution

- After aseptic dilution in sodium chloride solution:  
Chemical and physical stability of Rixathon diluted in 0.9% sodium chloride solution has been demonstrated for 30 days at 2°C - 8°C and subsequently 24 hours at room temperature ( $\leq 25^{\circ}\text{C}$ ).
- After aseptic dilution in glucose solution:  
Chemical and physical stability of Rixathon diluted in 5% glucose solution has been demonstrated for 24 hours at 2°C - 8°C and subsequently 12 hours at room temperature ( $\leq 25^{\circ}\text{C}$ ).

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

### **6.4 Special precautions for storage**

Store in a refrigerator (2°C – 8°C).

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

For storage conditions 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**

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

### Aseptic preparation

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

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

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

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

## **7.     MARKETING AUTHORISATION HOLDER**

Sandoz GmbH  
Biochemiestr. 10  
6250 Kundl  
Austria

## **8.     MARKETING AUTHORISATION NUMBER(S)**

Rixathon 100 mg concentrate for solution for infusion

EU/1/17/1185/001

EU/1/17/1185/002

Rixathon 500 mg concentrate for solution for infusion

EU/1/17/1185/003

EU/1/17/1185/004

## **9.     DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorization: 15 June 2017

## **10.    DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.