SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

BLITZIMA 100 mg concentrate for solution for infusion
BLITZIMA 500 mg concentrate for solution for infusion

WARNINGS

Infusion related reactions: Infusion related deaths (death within 24 hours of infusion) have been associated with rituximab. These events appear as manifestations of an infusion related complex and include hypoxia, pulmonary infiltrates, adult respiratory distress syndrome, myocardial infarction, ventricular fibrillation or cardiogenic shock. Nearly all fatal infusion related events occurred in relation to the first infusion.

Tumour lysis syndrome (TLS): In the setting of TLS, acute renal failure requiring dialysis, with instances of fatal outcome, has been associated with rituximab. Assessment of renal function and serum electrolytes are indicated in patients with a rapid decrease in tumour volume (see section 4.4).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Blitzima 100 mg concentrate for solution for infusion
Each mL contains 10 mg of rituximab.
Each 10 mL vial contains 100 mg of rituximab.

Blitzima 500 mg concentrate for solution for infusion
Each mL contains 10 mg of rituximab.
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.

Excipients with known effect
Each 10 mL vial contains 2,3 mmol (52,6 mg) sodium.
Each 50 mL vial contains 11,5 mmol (263,2 mg) sodium.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.
A clear to opalescent; colourless to pale yellow solution with pH of 6,3 – 6,8 and osmolality of 342 – 371 mOsmol/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BLITZIMA is indicated for the treatment of:
Non-Hodgkin's lymphoma (NHL)

- patients with stage III-IV follicular lymphoma who are chemo-resistant or are in their second or subsequent relapse after chemotherapy;
- previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy;
- patients with follicular lymphoma as maintenance treatment, after response to induction therapy;
- patients with high grade CD20-positive diffuse large B-cell non-Hodgkin's lymphoma in combination with

CHOP (Cyclophosphamide - C, Doxorubicin - H, Vincristine - O, Prednisolone - P) chemotherapy.

Rheumatoid arthritis
BLITZIMA 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 (DMARDs) 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.

Chronic lymphocytic leukaemia (CLL)
BLITZIMA in combination with fludarabine and cyclophosphamide is indicated for the treatment of patients with previously untreated and relapsed/refractory CLL. Only limited data are available on efficacy and safety for patients previously treated with monoclonal antibodies including **BLITZIMA** or patient's refractory to previous **BLITZIMA** plus chemotherapy.

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

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

4.2 Posology and method of administration
BLITZIMA 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 antihistamine, e.g. paracetamol and diphenhydramine, should always be given 30 to 60 minutes before each administration of **BLITZIMA**.

In patients with non-Hodgkin's lymphoma and CLL, premedication with glucocorticoids should be considered if **BLITZIMA** 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 x 109/L it is recommended to administer prednisone/prednisolone 100 mg intravenous shortly before infusion with **BLITZIMA** to decrease the rate and severity of acute infusion reactions and/or cytokine release syndrome.

In patients with rheumatoid arthritis, GPA or MPA or pemphigus vulgaris, premedication with 100 mg intravenous methylprednisolone should be completed 30 minutes prior to **BLITZIMA** 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 **BLITZIMA** (the last dose of methylprednisolone may be given on the same day as the first infusion of **BLITZIMA**). 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 **BLITZIMA** treatment.

Pneumocystis jirovecii pneumonia (PCP) prophylaxis is recommended for patients with GPA/MPA or PV during and following **BLITZIMA** treatment.

Posology
Non-Hodgkin's lymphoma
***Low-grade/CD20 positive or* non-Hodgkin's lymphoma**
a) Initial treatment, weekly for 4 doses: The recommended dosage of **BLITZIMA** used as a single agent/mono-therapy is 375 mg/m^2 body surface area (BSA), administered as an intravenous infusion once

weekly for four weeks.

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

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

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

e) ***Maintenance therapy***
Previously untreated follicular lymphoma:
The recommended dose of **BLITZIMA** used as a maintenance treatment for patients with previously untreated follicular lymphoma who have responded to induction treatment is: 375 mg/m^2 body surface area once every 2 months (starting 2 months after the last dose of induction therapy) until disease progression or for a maximum period of two years (12 infusions).
Relapsed/refractory follicular lymphoma:
The recommended dose of **BLITZIMA** used as a maintenance treatment for patients with relapsed/refractory follicular lymphoma who have responded to induction treatment is: 375 mg/m^2 body surface area once every 3 months (starting 3 months after the last dose of induction therapy) until disease progression or for a maximum period of two years.

High grade/CD20 positive or Diffuse large B cell non-Hodgkin's lymphoma
BLITZIMA should be used in combination with cyclophosphamide, doxorubicin (hydroxydaunomycin), vincristine (Oncovin), prednisolone (CHOP) chemotherapy. The recommended dosage is 375 mg/m^2 body surface area, administered on day 1 of each chemotherapy cycle for 8 cycles after intravenous infusion of the glucocorticoid component of CHOP. The other components of CHOP should be given after the administration of **BLITZIMA**.
First infusion: The recommended initial rate for infusion is 50 mg/hr, which can subsequently be escalated in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.
Subsequent infusions: Subsequent doses of **BLITZIMA** can be infused at an initial rate of 100 mg/hr and increased by 100 mg/hr at 30 minutes intervals, to a maximum of 400 mg/hr.
Alternative 90-minute subsequent infusions: Patients who do not experience a Grade 3 or 4 infusion-related adverse event with Cycle 1 are eligible for an alternative 90-minute subsequent infusion in Cycle 2. The alternative infusion rate can be started at a rate of 20 % of the total dose given in the first 30 minutes and the remaining 80 % of the total dose given over the next 60 minutes for a total infusion of 90 minutes. Patients who tolerate the first 90-minutes **BLITZIMA** infusion (Cycle 2) can continue to receive subsequent **BLITZIMA** infusions at the 90-minute rate for the remainder of the treatment regimen (through cycle 6 or cycle 8). Patients who have clinically significant cardiovascular disease or who have a circulating lymphocyte count > 5 000/mm3 before Cycle 2 should not receive the 90- minute infusion (see section 4.8).

Safety and efficacy of **BLITZIMA** 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 **BLITZIMA** are recommended. When **BLITZIMA** is given in combination with chemotherapy, standard dose reductions for the chemotherapeutic medicines should be applied.

Chronic lymphocytic leukaemia
Premedication consisting of an analgesic/anti-pyretic and an antihistamine, e.g. paracetamol and diphenhydramine, should always be given before each infusion of **BLITZIMA**.
Premedication with glucocorticoids should be considered if **BLITZIMA** is not given in combination with steroid-containing chemotherapy.

Prophylaxis with adequate hydration and administration of uricostatics starting 48 hours prior to start of therapy is recommended for CLL patients to reduce the risk of tumour lysis syndrome. For CLL patients whose lymphocyte counts are > 25 x 10^9/l it is recommended to administer prednisone/prednisolone 100 mg

intravenous shortly before infusion with **BLITZIMA** to decrease the rate and severity of acute infusion reactions and/or cytokine release syndrome.

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

Rheumatoid arthritis
Premedication consisting of an analgesic/anti-pyretic and an antihistamine, e.g. paracetamol and diphenhydramine, should always be given before each infusion of **BLITZIMA.**

Premedication with glucocorticoids should be administered in order to reduce the frequency and severity of infusion-related reactions. Patients should receive 100 mg IV methylprednisolone to be completed 30 minutes prior to each **BLITZIMA** infusion (see section 4.4).

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

A course of **BLITZIMA** consists of two 1 000 mg intravenous infusions. The recommended dosage of **BLITZIMA** 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. Patients may receive further courses no sooner than 16 weeks following the previous course.

Available data suggest that clinical response is usually achieved within 16 – 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.

First infusion: The recommended initial rate for infusion is 50 mg/hr; after the first 30 minutes, it can be escalated in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.
Second infusion: Subsequent doses of **BLITZIMA** can be infused at an initial rate of 100 mg/h and increased by 100 mg/hr increments at 30 minutes intervals, escalated, to a maximum of 400 mg/hr.

Granulomatosis with polyangiitis (Wegener's)(GPA) and microscopic polyangiitis (MPA)
Premedication consisting of an analgesic/anti-pyretic and an antihistamine, e.g. paracetamol and diphenhydramine, should always be given before each infusion of **BLITZIMA.**
Patients treated with **BLITZIMA** must be given the patient alert card with each infusion.
The recommended dosage of **BLITZIMA** for induction of remission therapy of granulomatosis with polyangiitis and microscopic polyangiitis is 375 mg/m^2 body surface area, administered as an intravenous infusion once weekly for 4 weeks (four infusions in total).

Methylprednisolone 1000 mg IV per day for 1 to 3 days is recommended in combination with **BLITZIMA** to treat severe vasculitis symptoms, followed by oral prednisolone 1 mg/kg/day (not to exceed 80 mg/day), and tapered as rapidly as possible per clinical need during and after **BLITZIMA** treatment.

First infusion: The recommended initial rate for infusion is 50 mg/hr; subsequently the rate can be escalated in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.
Subsequent infusions: Subsequent infusions of **BLITZIMA** can be started at a rate of 100 mg/h and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr.

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

Pemphigus vulgaris
The recommended dosage of **BLITZIMA** 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
Elderly
No dose adjustment is required in elderly patients (aged > 65 years).
Paediatric population
The safety and efficacy of **BLITZIMA** in children below 18 years has not been established. No data are available.

Method of administration
The prepared **BLITZIMA** solution should be administered as an IV infusion through a dedicated line. It should not be administered as an IV injection or bolus.
BLITZIMA is compatible with with 0,9 % sodium chloride (normal saline) or 5 % dextrose (D5W) solutions for infusion.

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 (IRRs) (see section 4.8) usually respond to a reduction in the rate of infusion. The infusion rate may be increased upon improvement of symptoms.
First infusion
The recommended initial rate for infusion is 50 mg/h; after the first 30 minutes, it can be escalated in 50 mg/h increments every 30 minutes, to a maximum of 400 mg/h.
Subsequent infusions
All indications
Subsequent doses of **BLITZIMA** 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 **BLITZIMA** 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 dysrhythmias, 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 rituximab or to murine proteins or to any of the excipients listed in section 6.1.
- Active, severe infections.
- Patients in a severely immunocompromised state.

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

- Hypersensitivity to the active substance rituximab or to murine proteins or to any of the excipients listed in section 6.1.
- Active, severe infections.
- Patients in a severely immunocompromised state.
- Severe heart failure (New York Heart Association Class IV) or severe, uncontrolled cardiac disease (see section 4.4).

4.4 Special warnings and precautions for use

Traceability

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

Tuberculosis (TB)

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

People initiating **BLITZIMA** / anti-TNF treatment, who initially tested negative for active or latent tuberculosis, should be systematically tested for latent TB infection during treatment with **BLITZIMA**, and preventive treatment instituted if indicated.

Progressive multifocal leukoencephalopathy (PML)

All patients treated with rituximab, as in **BLITZIMA**, for rheumatoid arthritis, pemphigus vulgaris, granulomatosis with polyangiitis and microscopic polyangiitis 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 PML.

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

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

The medical practitioner should be particularly alert to symptoms suggestive of PML that the patient may not notice (e.g. cognitive, neurological or psychiatric symptoms). Patients should also be advised to inform their partner or caregivers about their treatment, since they may notice symptoms that the patient is not aware of. If a patient develops PML the dosing of rituximab, as in **BLITZIMA**, must be permanently discontinued.
Following reconstitution of the immune system in immunocompromised patients with PML, stabilisation or improved outcome has been seen. It remains unknown if early detection of PML and suspension of rituximab therapy may lead to similar stabilisation or improved outcome.

Non-Hodgkin's lymphoma and chronic lymphocytic leukaemia

Infusion related reactions

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

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

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

Severe cytokine release syndrome is characterised by severe dyspnoea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. This syndrome may be associated with some features of ***tumour lysis syndrome*** such as hyperuricaemia, hyperkalaemia, hypocalcaemia, hyperphosphataemia, acute renal failure, elevated lactate dehydrogenase (LDH) and may be associated with acute respiratory failure and death. The acute respiratory failure may be accompanied by events such as pulmonary interstitial infiltration or oedema, visible on a chest X-ray. The syndrome frequently manifests itself within one or two hours of initiating the first infusion.
Patients with a history of pulmonary insufficiency or those with pulmonary tumour infiltration may be at greater risk of poor outcome and should be treated with increased caution. Patients who develop severe cytokine release syndrome should have their infusion interrupted immediately and should receive aggressive symptomatic treatment. Since initial improvement of clinical symptoms may be followed by deterioration, these patients should be closely monitored until tumour lysis syndrome and pulmonary infiltration have been resolved or ruled out. Further treatment of patients after complete resolution of signs and symptoms has rarely resulted in repeated severe cytokine release syndrome.
Patients with a high tumour burden or with a high number (≥ 25 x 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 x 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). 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. Medicines for the treatment of hypersensitivity reactions, e.g., epinephrine (adrenaline), antihistamines and glucocorticoids, should be available for immediate use in the event of an allergic reaction during administration of rituximab. Clinical manifestations of anaphylaxis may appear similar to clinical manifestations of the cytokine release syndrome. Reactions attributed to hypersensitivity have been reported less frequently than those attributed to cytokine release.

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

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

Cardiac disorders
Angina pectoris, cardiac dysrhythmias 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 x 10^9/l and/or platelet counts < 75 x 10^9/l as clinical experience in this population is limited. Rituximab has been used in 21 patients who underwent autologous bone marrow transplantation and other risk groups with a presumable reduced bone marrow function without inducing myelotoxicity.

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

Infections
Serious infections, including fatalities, can occur during therapy with rituximab (see section 4.8). Rituximab should not be administered to patients with an active, severe infection e.g. tuberculosis, sepsis and opportunistic infections (see section 4.3) or severely immunocompromised patients (e.g. where levels of CD4 or CD8 are very low).

Medical practitioners should exercise caution when considering the use of rituximab in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection (see section 4.8).
Patients being treated with rituximab should avoid exposure to patients with tuberculosis and contact with children and adults recently vaccinated with attenuated live vaccines.
Following rituximab therapy, patients who develop infection should be evaluated promptly and treated appropriately. Prior to initiating treatment with rituximab, it is recommended that immunoglobulin levels are determined.

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

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

Immunisations
The safety of immunisation with live viral vaccines, following rituximab therapy has not been studied for NHL and CLL patients and vaccination with live virus vaccines is not recommended. Patients treated with rituximab may receive non-live vaccinations. However with non-live vaccines response rates may be reduced. In a non-randomised study, 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 (GPA) and microscopic polyangiitis (MPA), 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. Premedication consisting of an analgesic/anti-pyretic medicine and an anti-histaminic medicine, should always be administered before each infusion of rituximab. In rheumatoid arthritis, preremedication with glucocorticoids should also be administered before each infusion of rituximab in order to reduce the frequency and severity of IRRs (see sections 4.2 and 4.8).

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

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

IRRs for patients with granulomatosis with polyangiitis and microscopic polyangiitis were similar to those seen for rheumatoid arthritis patients in clinical trials (see section 4.8).

Cardiac disorders
Angina pectoris, cardiac dysrhythmias 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). **BLITZIMA** should not be administered to patients with an active, severe infection (e.g. tuberculosis, sepsis and opportunistic infections, see section 4.3) or severely immunocompromised patients (e.g. where levels of CD4 or CD8 are very low). Medical practitioners should exercise caution when considering the use of rituximab in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection, e.g. hypogammaglobulinaemia (see section 4.8). It is recommended that immunoglobulin levels are determined prior to initiating treatment with rituximab.

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

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

Hepatitis B Infections
Cases of hepatitis B reactivation, including those with a fatal outcome, have been reported in rheumatoid arthritis~~,~~ granulomatosis with polyangiitis and microscopic polyangiitis patients receiving rituximab.

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

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

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

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

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

Patients treated with rituximab may receive non-live vaccinations. However, response rates to non-live vaccines may be reduced. In a randomised trial, patients with rheumatoid arthritis treated with rituximab and methotrexate had comparable response rates to tetanus recall antigen (39 % vs. 42 %), reduced rates to pneumococcal polysaccharide vaccine (43 % vs. 82 % to at least 2 pneumococcal antibody serotypes), and KLH neoantigen (47 % vs. 93 %), when given 6 months after rituximab as compared to patients only receiving methotrexate. Should non-live vaccinations be required whilst receiving rituximab therapy, these should be completed at least 4 weeks prior to commencing the next course of rituximab.

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

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

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

Malignancy
Immunomodulatory medicines 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.

Excipients
BLITZIMA contains 2,3 mmol (or 52,6 mg) sodium per 10 mL vial and 11,5 mmol (or 263,2 mg) sodium per 50 mL vial, equivalent to 2,6 % (for 10 mL vial) and 13, 2 % (for 50 mL vial) of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicines and other forms of interaction
Currently, there are limited data on possible interactions with **rituximab**.

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

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

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

In patients with rheumatoid arthritis, 283 patients received subsequent therapy with a biologic DMARD following rituximab. In these patients the rate of clinically relevant infection while on rituximab was 6,01 per 100 patient years compared to 4,97 per 100 patient years following treatment with the biologic DMARD.

4.6 Fertility, pregnancy and lactation
Safety and efficacy during pregnancy and lactation have not been established.
Pregnancy
IgG immunoglobulins are known to cross the placental barrier.
B cell levels in human neonates following maternal exposure to rituximab have not been studied in clinical trials. There are no adequate and well-controlled data from studies in pregnant women, however transient B-cell depletion and lymphocytopenia have been reported in some infants born to mothers exposed to rituximab during pregnancy. For these reasons **BLITZIMA** should not be administered to pregnant women unless the possible benefit outweighs the potential risk.
Women of childbearing potential
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 **BLITZIMA**.
Breastfeeding
Whether rituximab is excreted in human milk is not known. However, because maternal IgG is excreted in human milk, and rituximab was detectable in milk from lactating monkeys, women should not breastfeed while treated with **BLITZIMA** and for 12 months following **BLITZIMA** treatment.
Fertility
Animal studies did not reveal deleterious effects of rituximab on reproductive organs.

4.7 Effects on ability to drive and use machines
No studies on the effects of rituximab on the ability to drive and use machines have been performed.
Rituximab, as in **BLITZIMA**, may cause dizziness and influence the ability to drive and use machines.

4.8 Undesirable effects
Experience from non-Hodgkin's lymphoma (NHL) and chronic lymphocytic leukaemia (CLL)
a) Summary of the safety profile
The overall safety profile of rituximab in non-Hodgkin's lymphoma and CLL is based on data from patients from clinical trials and from post-marketing surveillance. These patients were treated either with rituximab monotherapy (as induction treatment or maintenance treatment following induction treatment) or in combination with chemotherapy.
The most frequently observed adverse drug reactions (ADRs) in patients receiving rituximab were IRRs which occurred in the majority of patients during the first infusion. The incidence of infusion related symptoms decreases substantially with subsequent infusions and is less than 1 % after eight doses of rituximab.
Infectious events (predominantly bacterial and viral) occurred in approximately 30 – 55 % of patients during clinical trials in patients with NHL and in 30 – 50 % of patients during clinical trials in patients with CLL.
The most frequent reported or observed serious adverse drug reactions were:
- IRRs (including cytokine-release syndrome, tumour-lysis syndrome)

- Infections
- Cardiovascular events

Other serious ADRs reported include hepatitis B reactivation and progressive multifocal leukoencephalopathy (PML).
See section 4.4.

b) Tabulated list of adverse reactions

The frequencies of ADRs reported with rituximab alone or in combination with chemotherapy are summarised below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), 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 post-marketing 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
Infections and infestations	bacterial infection, viral infections, +bronchitis	sepsis, +pneumonia, +febrile infection, +herpes zoster, +respiratory tract infection, fungal infections, infections of unknown aetiology, +acute bronchitis, +sinusitis, hepatitis B[1]		serious viral infection[2], *Pneumocystis jirovecii*	progressive multifocal leukoencephalopathy (PML)	
Blood and the lymphatic system disorders	neutropenia, leucopenia, +febrile neutropenia, +thrombocytopenia	anaemia, +pancytopenia, +granulocytopenia	coagulation disorders, aplastic anaemia, haemolytic anaemia, lymphadenopathy		transient increase in serum IgM levels[3]	late neutropenia[3]
Immune system disorders	infusion related reactions[4], angioedema	hypersensitivity		anaphylaxis	tumour lysis syndrome, cytokine release syndrome[4], serum sickness	infusion related acute reversible thrombocytopenia[4]
Metabolism and nutrition disorders		hyperglycaemia, weight decrease, peripheral oedema, face oedema, increased LDH, hypocalcaemia				

Psychiatric disorders			depression, nervousness			
Nervous system disorders		paraesthesia, hypoaesthesia, agitation, insomnia, vasodilatation, dizziness, anxiety	dysgeusia		peripheral neuropathy, facial nerve palsy[5]	cranial neuropathy, loss of other senses[5]
Eye disorders		lacrimation disorder, conjunctivitis			severe vision loss[5]	
Ear and labyrinth disorders		tinnitus, ear pain				hearing loss[5]
Cardiac disorders		+myocardial infarction[4 and 6], dysrhythmia, +atrial fibrillation, tachycardia, +cardiac disorder	+left ventricular failure, +supraventricular tachycardia, +ventricular tachycardia, +angina, +myocardial ischaemia, bradycardia	severe cardiac disorders[4 and 6]	heart failure[4 and 6]	
Vascular disorders		hypertension, orthostatic hypotension,			vasculitis (predominately cutaneous), leukocytoclastic vasculitis	
Respiratory, thoracic and mediastinal disorders		bronchospasm[4], respiratory disease, chest pain, dyspnoea, increased cough, rhinitis	asthma, bronchiolitis obliterans, lung disorder, hypoxia	interstitial lung disease[7]	respiratory failure[4]	lung infiltration
Gastrointestinal disorders	nausea	vomiting, diarrhoea, abdominal pain, dysphagia, stomatitis, constipation, dyspepsia, anorexia, throat irritation	abdominal enlargement		gastrointestinal perforation[7]	
Skin and subcutaneous tissue disorders	pruritus, rash, +alopecia	urticaria, sweating, night sweats, +skin disorder			severe bullous skin reactions, Stevens-Johnson Syndrome, toxic epidermal necrolysis (Lyell's Syndrome)[7]	

Musculoskeletal, connective tissue and bone disorders		hypertonia, myalgia, arthralgia, back pain, neck pain, pain				
Renal and urinary disorders					renal failure[4]	
General disorders and administration site conditions	fever, chills, asthenia, headache	tumour pain, flushing, malaise, cold syndrome, +fatigue, +shivering, +multi organ failure[4]	infusion site pain			
Investigations	decreased IgG levels					

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

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

[2] see also section infection below

[3] see also section haematologic adverse reactions below

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

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

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

[7] includes fatal cases

The following terms have been reported as adverse events during clinical trials, however, these terms 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 treatment.

Description of selected adverse reactions

Infections

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

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

Haematologic adverse reactions
In clinical trials with rituximab monotherapy given for 4 weeks, haematological abnormalities occurred in a minority of patients and were usually mild and reversible. Severe (grade 3/4) neutropenia was reported in 4,2 %, anaemia in 1,1 % and thrombocytopenia in 1,7 % of the patients. During rituximab maintenance treatment for up to 2 years, leucopenia (5 % vs. 2 %, grade 3/4) and neutropenia (10% vs. 4 %, grade 3/4) were reported at a higher incidence when compared to observation. The incidence of thrombocytopenia was low (< 1 %, grade 3/4) and was not different between treatment arms. During the treatment course in studies with rituximab in combination with chemotherapy, grade 3/4 leucopenia (R-CHOP 88 % vs. CHOP 79 %, R-FC 23 % vs. FC 12%), neutropenia (R-CVP 24 % vs. CVP 14 %; R-CHOP 97 % vs. CHOP 88 %, R-FC 30 % vs. FC 19 % in previously untreated CLL), pancytopenia (R-FC 3 % vs. FC 1 % in previously untreated CLL) were usually reported with higher frequencies when compared to chemotherapy alone. However, the higher incidence of neutropenia in patients treated with rituximab and chemotherapy was not associated with a higher incidence of infections and infestations compared to patients treated with chemotherapy alone. Studies in previously untreated and relapsed/refractory CLL have established that in up to 25 % of patients treated with R-FC neutropenia was prolonged (defined as neutrophil count remaining below $1x10^9$/l between day 24 and 42 after the last dose) or occurred with a late onset (defined as neutrophil count below $1x10^9$/l later than 42 days after last dose in patients with no previous prolonged neutropenia or who recovered prior to day 42) following treatment with rituximab plus FC. There were no differences reported for the incidence of anaemia. Some cases of late neutropenia occurring more than four weeks after the last infusion of rituximab were reported. In the CLL first-line study, Binet stage C patients experienced more adverse events in the R-FC arm compared to the FC arm (R-FC 83 % vs. FC 71 %). In the relapsed/refractory CLL study grade 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 dysrhythmia (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 dysrhythmias, predominantly supraventricular dysrhythmias 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 dysrhythmias either occurred in the context of a rituximab infusion or were associated with predisposing conditions such as fever, infection, acute myocardial infarction or pre-existing respiratory and cardiovascular disease. No difference between the R-CHOP and CHOP group was observed in the incidence of other grade 3 and 4

cardiac events including heart failure, myocardial disease and manifestations of coronary artery disease. In CLL, the overall incidence of grade 3 or 4 cardiac disorders was low both in the first-line study (4 % R-FC, 3 % FC) and in the relapsed/refractory study (4 % R-FC, 4 % FC).

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

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

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

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

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

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

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

Patient subpopulations - rituximab monotherapy
Elderly patients (≥ 65 years):
The incidence of ADRs of all grades and grade 3/4 ADR was similar in elderly patients compared to younger patients (< 65 years).

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

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

Patient subpopulations - rituximab combination therapy
Elderly patients (≥ 65 years)
The incidence of grade 3/4 blood and lymphatic adverse events was higher in elderly patients compared to

younger patients (< 65 years), with previously untreated or relapsed/refractory CLL.

Experience from rheumatoid arthritis

a) 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.

b) Tabulated list of adverse reactions

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

The most frequent adverse reactions considered due to receipt of rituximab were IRRs. The overall incidence of IRRs in clinical trials was 23 % with the first infusion and decreased with subsequent infusions. Serious IRRs were uncommon (0,5 % of patients) and were predominantly seen during the initial course. In addition to adverse reactions seen in RA clinical trials for rituximab, progressive multifocal leukoencephalopathy (PML) (see section and serum sickness-like reaction have been reported during post marketing experience.

Table 2: ADRs reported in clinical trials or during post-marketing surveillance in patients with rheumatoid arthritis receiving rituximab

System Organ Class	Very common	Common	Uncommon	Rare	Very rare	Not known
Infections and infestations	upper respiratory tract infection, urinary tract infections	bronchitis, sinusitis, gastroenteritis, tinea pedis			progressive multifocal leukoencephalopathy (PML), reactivation of hepatitis B	serious viral infection[1]
Blood and the lymphatic system disorders		Neutropenia[2]		late neutropenia[3]	serum sickness like reaction	
Immune system disorders ***AND*** ***General disorders and administration site conditions***	[4]infusion related reactions (hypertension, nausea, rash, pyrexia, pruritus, urticaria, throat irritation, hot flush, hypotension, rhinitis, rigors,		[4]infusion related reactions (generalised oedema, bronchospasm wheezing, laryngeal oedema, angioneurotic oedema, generalised			

	tachycardia, fatigue, oropharyngeal pain, peripheral oedema, erythema)		pruritus, anaphylaxis, anaphylactoid reaction)			
Metabolism and nutrition disorders		hypercholesterolemia				
Psychiatric disorders		depression, anxiety				
Nervous system disorders	headache	paraesthesia, migraine, dizziness, sciatica				
Cardiac disorders				Angina pectoris, atrial fibrillation, heart failure, myocardial infarction	Atrial flutter	
Gastrointestinal disorders		dyspepsia, diarrhoea, gastro-oesophageal reflux, mouth ulceration, upper abdominal pain				
Skin and subcutaneous tissue disorders		alopecia			toxic epidermal necrolysis (Lyell's syndrome), Stevens-Johnson syndrome[6]	
Musculoskeletal, connective tissue and bone disorders		arthralgia/musculoskeletal pain, osteoarthritis, bursitis				
Investigations	decreased IgM levels[5]		decreased IgG levels[5]			

[1] See also section infections below
[2] Frequency category derived from laboratory values collected as part of routine laboratory monitoring in clinical trials.
[3] Frequency category derived from post-marketing data.
[4] 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.
[5] Includes observations collected as part of routine laboratory monitoring.
[6] Includes fatal cases.

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

RA exacerbation and infections all of which were more frequent in the first 6 months of treatment.

c) 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 3 189 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 IV antibiotics, was approximately 4 per 100 patient years. The rate of serious infections did not show any significant increase following multiple courses of rituximab. Lower respiratory tract infections (including pneumonia) have been reported during clinical trials, at a similar incidence in the rituximab-arms compared to control arms.

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

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

The safety and effectiveness of rituximab in paediatric patients have not been established. 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 (Wegener's) (GPA) and microscopic polyangiitis (MPA)

a) Summary of the safety profile

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

b) Tabulated list of adverse reactions

The ADRs listed in Table 3 were all adverse events which occurred at an incidence of ≥ 5 % in the rituximab group.

Table 3: ADRs occurring at 6-months in ≥ 5 % of patients receiving rituximab, and at a higher frequency than the comparator group, in the pivotal clinical study

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

Back pain	10 %
Muscle weakness	5 %
Musculoskeletal pain	5 %
Pain in extremities	5 %
General disorders and administration site conditions	
Peripheral oedema	16 %
Investigations	
Decreased haemoglobin	6 %

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

Table 4: ADRs occurring in ≥ 5 % of patients receiving rituximab for maintenance treatment of GPA and MPA, and at a higher frequency than the comparator group.

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

The overall safety profile was consistent with the well-established safety profile for rituximab in approved autoimmune indications, including GPA/MPA. Overall, 4 % of patients in the rituximab arm experienced adverse events leading to discontinuation. Most adverse events in the rituximab arm were mild or moderate in intensity. No patients in the rituximab arm had fatal adverse events. The most commonly reported events considered as ADRs were infusion-related reactions and infections.
In a long-term observational safety study, 97 GPA/MPA patients received treatment with rituximab (mean of 8 infusions [range 1 to 28]) for up to 4 years, according to their physician's standard practice and discretion. The overall safety profile was consistent with the well-established safety profile of rituximab in GPA/MPA and no new adverse drug reactions were reported.

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

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

Malignancies
The incidence of malignancy in rituximab treated patients in the granulomatosis with polyangiitis and microscopic polyangiitis clinical study was 2,00 per 100 patient years at the study common closing date (when the final patient had completed the follow-up period).
On the basis of 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 post-marketing setting.

Hypogammaglobulinaemia
Hypogammaglobulinaemia (IgA, IgG or IgM below the lower limit of normal) has been observed in granulomatosis with polyangiitis and microscopic polyangiitis patients treated with rituximab. At 6 months, in the active-controlled, randomised, double-blind, multicentre, non-inferiority trial, in the rituximab group, 27 %, 58 % and 51 % of patients with normal immunoglobulin levels at baseline, had low IgA, IgG and IgM levels, respectively compared to 25 %, 50 % and 46 % in the cyclophosphamide group. There was no increased rate in overall infections or serious infections in patients with low IgA, IgG or IgM.

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 active controlled, randomised, double-blind, multicentre, non-inferiority trial of rituximab in granulomatosis with polyangiitis and microscopic polyangiitis, 24 % of patients in the rituximab group (single course) and 23 % of patients in the cyclophosphamide group developed CTC grade 3 or greater neutropenia. Neutropenia was not associated with an observed increase in serious infection in rituximab treated patients. The effect of multiple rituximab courses on the development of neutropenia in granulomatosis with polyangiitis and microscopic polyangiitis patients has not been studied in clinical trials.

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

a) Summary of the safety profile in PV Study 1 (Study ML22196) and PV Study 2 (Study WA29330)

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

In PV Study 2, a randomized, double-blind, double-dummy, active-comparator, multicenter study evaluating the efficacy and safety of rituximab compared with mycophenolate mofetil (MMF) in patients with moderate-to-severe PV requiring oral corticosteroids, 67 PV patients received treatment with rituximab (initial 1000 mg intravenous on Study Day 1 and a second 1000 mg intravenous on Study Day 15 repeated at Weeks 24 and 26) for up to 52 weeks.

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

b) Tabulated list of adverse reactions for PV Studies 1 and 2

Adverse reactions from PV Studies 1 and 2 are presented in Table 7. In PV Study 1, ADRs were defined as adverse events which occurred at a rate of ≥ 5 % among rituximab-treated PV patients, with a ≥ 2 % absolute difference in incidence between the rituximab-treated group and the standard-dose prednisone group up to month 24. No patients were withdrawn due to ADRs in Study 1. In PV Study 2, ADRs were defined as adverse events occurring in ≥ 5 % of patients in the rituximab arm and assessed as related.

Table 5: Adverse reactions in rituximab-treated pemphigus vulgaris patients in PV Study 1 (up to Month 24) and PV Study 2 (up to Week 52), or during post-marketing surveillance

System Organ Class	Very common	Common	Not known
Infections and infestations	upper respiratory tract infection	herpes virus infection herpes, zoster, oral herpes, conjunctivitis, nasopharyngitis, oral candidiasis, urinary tract infection	serious viral infection[1]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		skin papilloma	
Psychiatric disorders	persistent depressive disorder	major depression irritability	
Nervous system disorders	headache	dizziness	
Cardiac disorders		tachycardia	
Gastrointestinal disorders		abdominal pain upper	
Skin and subcutaneous tissue disorders	alopecia	pruritus, urticari skin disorder	

Musculoskeletal, connective tissue and bone disorders		musculoskeletal pain, arthralgia, back pain	
General disorders and administration site conditions		fatigue, asthenia, pyrexia	
Injury, poisoning and procedural complications	infusion-related reactions[2]		

[1] Observed during post-marketing surveillance. See also section infection below.
[2] Infusion-related reactions for PV Study 1 included symptoms collected on the next scheduled visit after each infusion, and adverse events occurring on the day of or one day after the infusion. The most common infusion-related reaction symptoms/Preferred Terms for PV Study 1 included headaches, chills, high blood pressure, nausea, asthenia and pain.

The most common infusion-related reaction symptoms/Preferred Terms for PV Study 2 were dyspnoea, erythema, hyperhidrosis, flushing/hot flush, hypotension/low blood pressure and rash/rash pruritic.

c) Description of selected adverse reactions

Infusion-related reactions

In PV Study 1, infusion-related reactions 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.

In PV Study 2, IRRs occurred primarily at the first infusion and the frequency of IRRs decreased with subsequent infusions: 17,9 %, 4,5 %, 3 % and 3 % of patients experienced IRRs at the first, second, third, and fourth infusions, respectively. In 11/15 patients who experienced at least one IRR, the IRRs were Grade 1 or 2. In 4/15 patients, Grade ≥ 3 IRRs were reported and led to discontinuation of rituximab treatment; three of the four patients experienced serious (life-threatening) IRRs. Serious IRRs occurred at the first (2 patients) or second (1 patient) infusion and resolved with symptomatic treatment.

Infections

In PV Study 1, 14 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).

In PV Study 2, 42 patients (62,7 %) in the rituximab arm experienced infections. The most common infections in the rituximab group were upper respiratory tract infection, nasopharyngitis, oral candidiasis and urinary tract infection. Six patients (9 %) in the rituximab arm experienced serious infections.

In the post marketing setting, serious viral infection has been reported in PV patients with rituximab.

Laboratory abnormalities

PV Study 2, in the rituximab arm, transient decreases in lymphocyte count, driven by decreases in the peripheral T-cell populations, as well as a transient decrease in phosphorus level were very commonly observed post-infusion. These were considered to be induced by intravenous methylprednisolone premedication infusion.

In PV Study 2, low IgG levels were commonly observed, and low IgM levels were very commonly observed; however, there was no evidence of an increased risk of serious infections after the development of low IgG or IgM.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.
Reporting can also be done directly to Adcock Ingram Limited at Adcock.aereports@adcock.com.

4.9 Overdose
Limited experience with doses higher than the approved dose of intravenous rituximab formulation is available from clinical trials in humans. The highest intravenous dose of rituximab tested in humans to date is 5 000 mg (2 250 mg/m^2), tested in a dose escalation study in patients with CLL. No additional safety signals were identified.

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

In the post marketing setting five cases of rituximab overdose have been reported. Three cases had no reported adverse event. The two adverse events that were reported were flu-like symptoms, with a dose of 1,8 g of rituximab and fatal respiratory failure, with a dose of 2 g of rituximab.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacological classification: A 26 Cytostatic agents
Pharmacotherapeutic group: antineoplastic agents, monoclonal antibodies, ATC code: L01X C02
Blitzima is a biosimilar medicine.

Rituximab is a chimeric mouse/human monoclonal antibody that binds specifically to the trans-membrane antigen CD20.

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

The Fab domain of rituximab binds to the CD20 antigen on B lymphocytes and the Fc domain can recruit immune effector functions to mediate B cell lysis. Possible mechanisms of effector-mediated cell lysis include complement-dependent cytotoxicity (CDC) resulting from C1q binding, and antibody-dependent cellular cytotoxicity (ADCC) mediated by one or more of the Fcγ receptors on the surface of granulocytes, macrophages and NK cells. Rituximab binding to CD20 antigen on B lymphocytes has also been demonstrated to induce cell death via apoptosis. Rituximab binding was observed on lymphoid cells in the thymus, the white pulp of the spleen, and a majority of B lymphocytes in peripheral blood and lymph nodes. Little or no binding was observed in the non-lymphoid tissues examined.

In clinical studies, 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 (Wegener's)(GPA) or and Microscopic polyangiitis (MPA), the number of peripheral blood B cells decreased to <10 cells/µl after two weekly infusions of rituximab 375 mg/m^2, and remained at that level in most patients up to the 6 month time point. The majority of patients (81 %) showed signs of B cell return, with counts >10 cells/µl by month 12, increasing to 87 % of patients by month 18.

5.2 Pharmacokinetic properties

Non-Hodgkin's lymphoma

Based on a population pharmacokinetic analysis in 298 NHL patients who received single or multiple infusions of rituximab as a single agent or in combination with CHOP therapy (applied rituximab doses ranged from 100 to 500 mg/m^2), the typical population estimates of nonspecific clearance (CL1), specific clearance (CL2) likely contributed by B cells or tumour burden, and central compartment volume of distribution (V1) 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 CL2 of rituximab in data from 161 patients given 375 mg/m^2 as an intravenous infusion for 4 weekly doses.

Age, gender and WHO performance status had no effect on the pharmacokinetics of rituximab. This analysis suggests that dose adjustment of rituximab with any of the tested covariates is not expected to result in a meaningful reduction in its pharmacokinetic variability.

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

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

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

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. 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 (IV) doses of 500 mg and 1 000 mg on Days 1 and 15 in four studies. In all these studies, rituximab pharmacokinetics were dose proportional over the limited dose range studied. Mean C_{max} for serum rituximab following first infusion ranged from 157 to 171 µg/mL for 2 x 500 mg dose and ranged from 298 to 341 µg/mL for 2 x 1 000 mg dose. Following second infusion, mean C_{max} ranged from 183 to 198 µg/mL for the 2 × 500 mg dose and ranged from 355 to 404 µg/mL for the 2 × 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 × 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 IV doses of 500 mg and 1 000 mg upon re-treatment in the second course. Mean C_{max} for serum rituximab following first infusion was 170 to 175 µg/mL for 2 x 500 mg dose and 317 to 370 µg/mL for 2 x 1 000 mg dose. C_{max} following second infusion was 207 µg/mL for the 2 x 500 mg dose and ranged from 377 to 386 µg/mL for the 2 x 1 000 mg dose. Mean terminal elimination half-life after the second infusion, following the second course, was 19 days for 2 x 500 mg dose and ranged from 21 to 22 days for the 2 x 1 000 mg dose. PK parameters for rituximab were comparable over the two treatment courses.

The pharmacokinetic (PK) parameters in the anti-TNF inadequate responder population, following the same dosage regimen (2 x 1 000 mg, IV, 2 weeks apart), were similar with a mean maximum serum concentration of 369 mg/mL and a mean terminal half-life of 19,2 days.

Chronic lymphocytic leukaemia

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

Granulomatosis with polyangiitis and microscopic polyangiitis
Based on the population pharmacokinetic analysis of data in 97 patients with granulomatosis with polyangiitis and microscopic polyangiitis who received 375 mg/m^2 rituximab once weekly for four doses, the estimated median terminal elimination half-life was 23 days (range, 9 to 49 days).Rituximab mean clearance and volume of distribution were 0,313 l/day (range, 0,116 to 0,726 l/day) and 4,50 l (range 2,25 to 7,39 l) respectively. The PK parameters of rituximab in these patients appear similar to what has been observed in rheumatoid arthritis patients.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Polysorbate 80, sodium chloride, tri-sodium citrate dihydrate, water for injections.

6.2 Incompatibilities
No incompatibilities between rituximab and polyvinyl chloride or polyethylene bags or infusion sets have been observed.

6.3 Shelf life
Unopened vial
4 years
Store at 2 °C to 8 °C in a refrigerator. Keep the vial in the outer carton in order to protect from light.

Diluted product
The prepared infusion solution of rituximab is physically and chemically stable for 24 hours at 2 °C to 8 °C and subsequently 12 hours at room temperature (not more than 30 °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 to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage
For storage conditions, see section 6.3.

6.5 Nature and contents of container
BLITZIMA 100 mg: Clear, colourless, type I glass vial with a chlorobutyl rubber stopper and an aluminium seal with a yellow flip-off cap containing 100 mg of rituximab in 10 mL. Pack of 2 vials.

BLITZIMA 500 mg: Clear, colourless, type I glass vial with a chlorobutyl rubber stopper and an aluminium seal with a dark grey flip-off cap containing 500 mg of rituximab in 50 mL. Pack of 1 vial.

6.6 Special precautions for disposal and other handling
BLITZIMA is provided in sterile, preservative-free, non-pyrogenic, single use vials.

Aseptically withdraw the necessary amount of **BLITZIMA** 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 % dextrose 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 **BLITZIMA** does not contain any anti-microbial preservative or bacteriostatic agents, aseptic technique must be observed. Parenteral medicines should be inspected visually for particulate matter and discolouration prior to administration.

Any unused medicinal product or waste material should be disposed of.

7. HOLDER OF CERTIFICATE OF REGISTRATION
Adcock Ingram Limited
1 New Road
Erand Gardens
Midrand, 1685
Customer Care: 0860 ADCOCK / 232625

8. REGISTRATION NUMBER(S)
BLITZIMA 100 mg: 53/26/0506
BLITZIMA 500 mg: 53/26/0507

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
25 August 2020

10. DATE OF REVISION OF THE TEXT
17 January 2025