SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

RITUXIMAB 100 EQUITY, concentrate for solution for infusion.

RITUXIMAB 500 EQUITY, concentrate for solution for infusion.

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

Tumour Lysis Syndrome (TLS): Acute renal failure requiring dialysis with instances of fatal outcome has been reported in the setting of TLS. Assessment of serum electrolytes and renal function is indicated in patients with rapid decreases in tumour volume (see section 4.4).

Severe mucocutaneous reactions, some with fatal outcomes: Sever, including fatal, mucocutaneous reactions can occur in patients receiving RITUXIMAB EQUITY (see section 4.4).

Hepatitis B Virus (HBV) Reactivation: HBV reactivation can occur in patients treated with RITUXIMAB EQUITY, in some cases resulting in fulminant hepatitis, hepatic failure and death. Screen all patients for HBV infection before treatment initiation and monitor patients during and after treatment with RITUXIMAB EQUITY. Discontinue RITUXIMAB EQUITY and concomitant medicines in the event of HBV reactivation (see section 4.4).

Progressive multifocal leukoencephalopathy, resulting in death: Progressive multifocal leukoencephalopathy (PML), including fatal PML, can occur in patients receiving RITUXIMAB EQUITY (see section 4.4 and 4.8).

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

RITUXIMAB EQUITY (see section 4.3 and 4.4).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

RITUXIMAB 100 EQUITY concentrate for solution for infusion:

Each mL contains 10 mg of rituximab

Each 10 mL vial contains 100 mg of rituximab

RITUXIMAB 500 EQUITY 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 effects

Each 10 mL vial contains 1,8 mmol (or 41,3 mg) sodium. Each 50 mL vial contains 8,9 mmol (or 205,8 mg) sodium.

RITUXIMAB EQUITY is sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear or slightly opalescent, colourless to light yellow liquid free of visible particles, with a pH of 6,2 – 6,8 and osmolality of 324 – 396 mOsmol/g.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Non-Hodgkin's lymphoma (NHL)

Rituximab Equity is indicated for the treatment of:

- patients with relapsed or chemo-resistant low-grade or follicular, CD20-positive, B-cell non-Hodgkin's lymphoma
- previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy
- patients with follicular lymphoma as maintenance treatment, after response to induction therapy
- patients with high grade CD20-positive diffuse large B-cell non-Hodgkin's lymphoma in combination with CHOP (Cyclophosphamide - C, Doxorubicin - H, Vincristine - O, Prednisone - P) chemotherapy

Chronic Lymphocytic Leukaemia

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

Rheumatoid arthritis

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

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

Rituximab Equity 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).

4.2 Posology and method of administration

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

Pre-medication consisting of an anti-pyretic and an antihistaminic, e.g. paracetamol and diphenhydramine, should always be administered 30 to 60 minutes prior to each infusion of Rituximab Equity.

Pre-medication with glucocorticoids should also be considered, particularly if Rituximab Equity is not given in combination with steroid-containing chemotherapy.

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

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

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

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

d) Combination therapy: The recommended dosage of Rituximab Equity in combination with chemotherapy for induction treatment of previously untreated or relapsed/refractory patients with follicular NHL is 375 mg/m^2 BSA per cycle for 8 cycles (21 days/cycle).

Rituximab Equity should be administered on day 1 of each chemotherapy cycle, after IV administration of the glucocorticoid component of the chemotherapy, if applicable.

e) Maintenance therapy:

Previously untreated patients after response to induction treatment with R-CHOP may receive maintenance therapy with Rituximab Equity given at 375 mg/m^2 BSA once every 2 months until disease progression or for a

maximum period of two years (12 infusions). Efficacy has not been demonstrated in patients who previously received Rituximab Equity plus CVP or with FCM.

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

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

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

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 Rituximab Equity can be infused at an initial rate of 100 mg/hr, and increased by 100 mg/hr increments at 30-minute intervals, to a maximum of 400 mg/hr.

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 time of 90 minutes.

Patients who tolerate the first 90-minute Rituximab Equity infusion (Cycle 2) can continue to receive subsequent Rituximab Equity 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/mm^3 before Cycle 2 should not receive the 90-minute infusion.

Dosage adjustments during treatment

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

Chronic Lymphocytic Leukaemia (CLL):

Pre-medication consisting of an analgesic/anti-pyretic (e.g. paracetamol) and an antihistaminic (e.g. diphenhydramine) should always be administered before each infusion of Rituximab Equity. Pre-medication with glucocorticoids should also be considered, particularly if Rituximab Equity 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 $10^9/\ell$ it is recommended to administer prednisone/prednisolone 100 mg IV shortly before infusion with Rituximab Equity to decrease the rate and severity of acute infusion reactions and/or cytokine release syndrome.

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

Rheumatoid arthritis (RA):

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

Pre-medication consisting of an analgesic/anti-pyretic (e.g. paracetamol) and an antihistaminic (e.g. diphenhydramine) should always be administered before each infusion of Rituximab Equity. Pre-medication

with glucocorticoids should also 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 Rituximab Equity infusion. See section 4.4.

A course of Rituximab Equity consists of two 1 000 mg IV infusions. The recommended dosage of Rituximab Equity is 1 000 mg by IV infusion followed two weeks later by the second 1 000 mg IV infusion.

The need for further courses should be evaluated 24 weeks following the previous course with retreatment given based on residual or disease activity returning to a level above a DAS28-ESR of 2,6 (treatment to remission). Patients may receive further courses no sooner than 16 weeks following the previous course.

First infusion of each course: 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 of each course: Subsequent doses of Rituximab Equity can be infused at an initial rate of 100 mg/hr, and increased by 100 mg/hr increments at 30 minutes intervals, to a maximum of 400 mg/hr.

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

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

Pre-medication consisting of an analgesic/anti-pyretic (e.g. paracetamol) and an antihistaminic (e.g. diphenhydramine) should always be administered before each infusion of Rituximab Equity.

Adult induction of remission

The recommended dosage of Rituximab Equity for induction of remission therapy in adult patients with GPA and MPA is 375 mg/m^2 BSA, administered as an IV infusion once weekly for 4 weeks (four infusions in total).

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

First infusion: The recommended initial infusion rate for Rituximab Equity 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 Rituximab Equity can be started at a rate of 100 mg/hr and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr.

Adult maintenance treatment

Following induction of remission with Rituximab Equity, maintenance treatment in adult patients with GPA and MPA should be initiated no sooner than 16 weeks after the last Rituximab Equity infusion.

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

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

Pneumocystis jiroveci pneumonia (PCP) prophylaxis is recommended for patients with GPA and MPA during and following Rituximab Equity treatment, as appropriate.

Special populations

Elderly

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

Paediatric population

The safety and efficacy of Rituximab Equity in children and adolescents have not been established.

Method of administration

The prepared Rituximab Equity solution should be administered as an intravenous infusion through a dedicated line. It should not be administered as an intravenous push or bolus.

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

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

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

4.3 Contraindications

- Hypersensitivity to the active substance or to murine proteins, or to any of the other excipients listed in section 6.1.
- Active, severe infections (see section 4.4).

- Patients in a severely immunocompromised state.
- Severe heart failure (New York Heart Association Class IV) or severe, uncontrolled cardiac disease (see section 4.4 and 4.8 regarding other cardiovascular diseases).

4.4 Special warnings and precautions for use

Traceability

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

Screening for tuberculosis should be undertaken prior to commencement of treatment with Rituximab Equity. A diagnosis of any form of active tuberculosis should be explicitly excluded in patients considered for treatment with Rituximab Equity. Furthermore, a history of previous tuberculosis, HIV-infection, or a diagnosis of latent tuberculosis 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 Rituximab Equity.

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

<u>Progressive multifocal leukoencephalopathy (PML)</u>

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

Fatal PML have been reported following the use of Rituximab Equity. 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 medical practitioner 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 Equity 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 Equity therapy may lead to similar stabilisation or improved outcome.

Non-Hodgkin’s lymphoma and chronic lymphocytic leukaemia

Infusion-related reactions

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

This set of reactions which includes syndrome of cytokine release, tumour lysis syndrome and anaphylactic and

hypersensitivity reactions are described below.

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

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

Patients with a high tumour burden or with a high number ($\geq 25 \times 10^9$/L) of circulating malignant cells such as patients with CLL and mantle cell lymphoma, who may be at higher risk of especially severe cytokine release syndrome, should be treated with extreme caution and only when other therapeutic alternatives have been

exhausted. These patients should be very closely monitored throughout the first infusion. Consideration should be given to the use of a reduced infusion rate for the first infusion in these patients or a split dosing over two days during the first cycle and any subsequent cycles if the lymphocyte count is still > 25 x 10^9/L.

Infusion-related adverse reactions of all kinds have been observed in 77 % of patients treated with Rituximab Equity (including cytokine release syndrome accompanied by hypotension and bronchospasm in 10 % of patients) (see section 4.8). These symptoms are usually reversible with interruption of Rituximab Equity 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 Equity. Clinical manifestations of anaphylaxis may appear similar to clinical manifestations of the cytokine release syndrome (described above). Reactions attributed to hypersensitivity have been reported less frequently than those attributed to cytokine release.

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

Since hypotension may occur during Rituximab Equity administration, consideration should be given to withholding anti-hypertensive medicines 12 hours prior to the Rituximab Equity 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 Equity. Therefore, patients with a history of cardiac disease and/or cardiotoxic chemotherapy should be monitored closely.

Haematological toxicities

Although Rituximab Equity 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, as contained in Rituximab Equity, has been used in 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 Equity therapy.

Infections

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

Medical practitioners should exercise caution when considering the use of Rituximab Equity 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 treated with Rituximab Equity should avoid exposure to patients with tuberculosis.

Cases of hepatitis B reactivation have been reported in subjects receiving Rituximab Equity including fulminant

hepatitis with fatal outcome. The majority of these subjects were also exposed to cytotoxic chemotherapy. Limited information in relapsed/refractory CLL patients suggests that Rituximab Equity 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 Equity. 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 Equity. Patients with positive hepatitis B serology (either HBsAg or HBcAb) should consult liver disease experts before start of treatment. Patients with evidence of current or prior HBV infection should be monitored for clinical and laboratory signs of hepatitis or HBV reactivation during and for several months following Rituximab Equity therapy. HBV reactivation has been reported up to 24 months following completion of Rituximab Equity therapy. Local medical standards should be followed to prevent hepatitis B reactivation.

Cases of progressive multifocal leukoencephalopathy (PML) have been reported during post-marketing use of rituximab, as contained in Rituximab Equity, in NHL and CLL (see section 4.8). The majority of patients had received rituximab in combination with chemotherapy or as part of a haematopoietic stem cell transplant.

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

False negative serologic testing of infections

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

Immunisations

The safety of immunisation with live viral vaccines, following Rituximab Equity therapy has not been studied

for NHL and CLL patients and vaccination with live virus vaccines is not recommended. Patients treated with Rituximab Equity may receive non-live vaccinations. However, with non-live vaccines response rates may be reduced. Patients with relapsed low-grade NHL who received rituximab monotherapy, as contained in Rituximab Equity, 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 Equity.

Patients treated with Rituximab Equity should avoid contact with children and adults recently vaccinated with attenuated live vaccines.

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 Equity, treatment should be permanently discontinued.

<u>Rheumatoid arthritis, granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA)</u>

Methotrexate (MTX) naïve populations with rheumatoid arthritis

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

Infusion-related reactions

Rituximab Equity is associated with infusion-related reactions (IRRs), which may be related to release of

cytokines and/or other chemical mediators.

Severe IRRs with fatal outcome have been reported in rheumatoid arthritis patients in the post-marketing setting. In rheumatoid arthritis most infusion-related events reported in clinical trials were mild to moderate in severity. The most frequent 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 Equity 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 Equity. In most cases, the infusion can be resumed at a 50 % reduction in rate (e.g. from 100 mg/hr to 50 mg/hr) 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 Equity.

There are no data on the safety of Rituximab Equity in patients with moderate heart failure (NYHA class III) or severe, uncontrolled cardiovascular disease. In patients treated with Rituximab Equity, 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 Equity and patients closely monitored during administration. Since hypotension may occur during Rituximab Equity infusion, consideration should be given to withholding anti-hypertensive medicine 12 hours prior to the Rituximab Equity 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 Equity. 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 Equity and the knowledge that B-cells play an important role in maintaining normal immune response, patients have an increased risk of infection following Rituximab Equity therapy (see section 5.1). Serious infections, including fatalities, can occur during therapy with Rituximab Equity (see section 4.8). Rituximab Equity 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 Equity 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 Equity.

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

Less frequently, cases of fatal progressive multifocal leukoencephalopathy (PML) have been reported following

use of Rituximab Equity for the treatment of rheumatoid arthritis and autoimmune diseases including Systemic Lupus Erythematosus (SLE) and vasculitis.

Patients treated with Rituximab Equity should avoid exposure to patients with tuberculosis.

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

False negative serologic testing of infections

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

Hepatitis B Infections

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

Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with Rituximab Equity. 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 Equity. Patients with positive hepatitis B serology (either HBsAg or HBcAb) should consult liver disease experts before start of treatment. Patients with evidence of current or prior HBV infection should be monitored for clinical and laboratory signs of hepatitis or HBV reactivation during and for several months following Rituximab Equity therapy. HBV reactivation has been reported up to 24 months following completion of Rituximab Equity therapy. Local medical standards should be followed to prevent hepatitis B reactivation.

Late neutropenia

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

Immunisation

Medical practitioners should review the patient's vaccination status and patients should, if possible, be brought up-to-date with all immunisations in agreement with current immunisation guidelines prior to initiating Rituximab Equity therapy. Vaccination should be completed at least 4 weeks prior to first administration of Rituximab Equity.

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

Patients treated with Rituximab Equity may receive non-live vaccinations. However, response rates to non-live vaccines may be reduced. In a clinical trial, patients with rheumatoid arthritis treated with Rituximab Equity 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 Equity, as compared to patients only receiving methotrexate. Should non-live vaccinations be required whilst receiving Rituximab Equity therapy, these should be completed at least 4 weeks prior to commencing the next course of Rituximab Equity.

In the overall experience of Rituximab Equity 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.

Patients treated with Rituximab Equity should avoid contact with children and adults recently vaccinated with attenuated live vaccines.

Concomitant/sequential use of other DMARDs in rheumatoid arthritis

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

There are limited data to fully assess the safety of the sequential use of other DMARDs (including TNF inhibitors and other biologics) following Rituximab Equity (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 Equity, however patients should be closely observed for signs of infection if biologic medicines and/or DMARDs are used following Rituximab Equity therapy.

Malignancy

Immunomodulatory medicines may increase the risk of malignancy. However, available data do not suggest an increased risk of malignancy for Rituximab Equity used in autoimmune indications beyond the malignancy risk already associated with the underlying autoimmune condition. However, the possible risk for the development of solid tumours cannot be excluded at this time.

Excipients

Rituximab Equity contains 1,8 mmol (or 41,3 mg) sodium per 10 mL vial and 8,9 mmol (or 205,8 mg) sodium

per 50 mL vial, equivalent to 2,1 % (for 10 ml vial) and 10,3 % (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 medicine interactions with Rituximab Equity.

In CLL patients, co-administration with Rituximab Equity 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 Equity.

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

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

In patients with rheumatoid arthritis receiving subsequent therapy with a biologic DMARD following Rituximab Equity, the rate of clinically relevant infection while on Rituximab Equity 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 in pregnancy and lactation has not been established

Women of childbearing potential / Contraception in males and females

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

Pregnancy

IgG immunoglobulins are known to cross the placental barrier.

B-cell levels in human neonates following maternal exposure to Rituximab Equity 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, as contained in Rituximab Equity, during pregnancy. Similar effects have been observed in animal studies (see section 5.3). For these reasons Rituximab Equity should not be administered to pregnant women.

Breastfeeding

Whether rituximab is excreted in human milk is not known. However, because maternal IgG is excreted in human milk, women should not breastfeed while treated with Rituximab Equity and for 12 months following Rituximab Equity 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 Equity on the ability to drive and use machines have been performed, although the pharmacological activity and adverse reactions reported to date suggest that Rituximab Equity would have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

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

Summary of the safety profile

The overall safety profile of Rituximab Equity 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 (as contained in Rituximab Equity) 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 (as contained in Rituximab Equity) were infusion-related reactions (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 Equity.

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

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

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

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

Tabulated list of adverse reactions

The frequencies of ADRs reported with Rituximab Equity, alone or in combination with chemotherapy are summarised in Table 1.

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 Equity monotherapy/maintenance or in combination with

chemotherapy

System organ class	Frequent	Less frequent	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*, PML	Enteroviral meningoencephalitis[2, 3]
Blood and lymphatic system disorders	Neutropenia, leukopenia, [+]febrile neutropenia, [+]thrombocytopenia, anaemia, [+]pancytopenia, [+]granulocytopenia	Coagulation disorders, aplastic anaemia, haemolytic anaemia, lymphadenopathy, transient increase in serum IgM levels[4]	Late neutropenia[4]
Immune system disorders	Infusion-related reactions[5], angioedema, hypersensitivity	Anaphylaxis, tumour lysis syndrome, cytokine release syndrome[5], serum sickness	Infusion-related acute reversible thrombocytopenia [5]
Metabolism and nutrition disorders	Hyperglycaemia, weight decrease,		

	peripheral oedema, face oedema, increased LDH, hypocalcaemia		
Psychiatric disorders		Depression, nervousness	
Nervous system disorders	Paraesthesia, hypoaesthesia, agitation, insomnia, vasodilatation, dizziness, anxiety	Dysgeusia, peripheral neuropathy, facial nerve palsy[6]	Cranial neuropathy, loss of other senses[6]
Eye disorders	Lacrimation disorder, conjunctivitis	Severe vision loss[6]	
Ear and labyrinth disorders	Tinnitus, ear pain		Hearing loss[6]
Cardiac disorders	[+]Myocardial infarction[5, 7], dysrhythmia, [+]atrial fibrillation, tachycardia, [+]cardiac disorder	[+]Left ventricular failure, [+]supraventricular tachycardia, [+]ventricular tachycardia, [+]angina, [+]myocardial ischaemia, bradycardia, severe cardiac disoders[5, 7], heart failure[5, 7]	
Vascular disorders	Hypertension, orthostatic hypotension, hypotension	Vasculitis (predominately cutaneous), leukocytoclastic vasculitis	

Respiratory, thoracic and mediastinal disorders	Bronchospasm[5], respiratory disease, chest pain, dyspnoea, increased cough, rhinitis	Asthma, bronchiolitis obliterans, lung disorder, hypoxia, interstitial lung disease[8], respiratory failure[5]	Lung infiltration
Gastrointestinal disorders	Nausea, vomiting, diarrhoea, abdominal pain, dysphagia, stomatitis, constipation, dyspepsia, anorexia, throat irritation	Abdominal enlargement, gastrointestinal perforation[8]	
Skin and subcutaneous tissue disorders	Pruritus, rash, [+]alopecia, urticaria, sweating, night sweats, [+]skin disorder	Severe bullous skin reactions, Stevens-Johnson Syndrome, toxic epidermal necrolysis (Lyell's Syndrome)[8]	
Musculoskeletal and connective tissue disorders	Hypertonia, myalgia, arthralgia, back pain, neck pain, pain		
Renal and urinary disorders		Renal failure[5]	
General disorders and administration site conditions	Fever, chills, asthenia, headache, tumour pain, flushing, malaise, cold syndrome, [+]fatigue, [+]shivering, [+]multi-	Infusion site pain	

	organ failure[5]		
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] observed during post-marketing surveillance

[4] see also section haematologic adverse reactions below

[5] see also section infusion-related reactions below. Fatal cases reported less frequently

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

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

[8] includes fatal cases

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

Signs and symptoms suggestive of an infusion-related reaction were reported in more than 50 % of patients in clinical trials, and were predominantly seen during the first infusion, usually in the first one to two hours. These symptoms mainly comprised fever, chills and rigors. Other symptoms included flushing, angioedema, bronchospasm, vomiting, nausea, urticaria/rash, fatigue, headache, throat irritation, rhinitis, pruritus, pain, tachycardia, hypertension, hypotension, dyspnoea, dyspepsia, asthenia and features of tumour lysis syndrome. Severe infusion-related reactions (such as bronchospasm, hypotension) occurred in up to 12 % of the cases.

Additional reactions reported in some cases were myocardial infarction, atrial fibrillation, pulmonary oedema and acute reversible thrombocytopenia. Exacerbations of pre-existing cardiac conditions such as angina pectoris or congestive heart failure or severe cardiac disorders (heart failure, myocardial infarction, atrial fibrillation), pulmonary oedema, multi-organ failure, tumour lysis syndrome, cytokine release syndrome, renal failure, and respiratory failure were reported at lower or unknown frequencies. The incidence of infusion-related symptoms decreased substantially with subsequent infusions and is < 1 % of patients by the eighth cycle of Rituximab Equity-containing treatment.

Description of selected adverse events

Infections

Rituximab, as contained in Rituximab Equity, induces B-cell depletion in about 70 – 80 % of patients, but was associated with decreased serum immunoglobulins only in a minority of patients. Bacterial, viral, fungal and unknown aetiology infections irrespective of causal assessment, occurred in 30,3 % 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 Equity monotherapy. Higher frequencies of infections overall, including grade 3 or 4 infections, were observed during Rituximab Equity 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 Equity treatment. The majority of patients had received rituximab, as contained in Rituximab Equity, 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)), enterovirus (meningoencephalitis) and hepatitis C virus (see section 4.4). 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 Equity 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 Equity-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 Equity 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 Equity maintenance treatment for up to 2 years, leukopenia (5 % vs. 2 %, grade 3/4) and neutropenia (10 % vs. 4 %, grade 3/4) were reported at a higher incidence when compared to observation. The incidence of thrombocytopenia was low (< 1 %, grade 3/4) and was not different between treatment arms. In approximately half of the patients with available data on B-cell recovery after the end of Rituximab Equity induction treatment, it took 12 months or more for their B-cell levels to return to normal values.

During the treatment course in studies with Rituximab Equity in combination with chemotherapy, grade 3/4 leukopenia (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 Equity 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 Equity 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 Equity 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 Equity in patients with Waldenstrom's macroglobulinaemia, transient increases in serum IgM levels have been observed following treatment initiation, which may be associated with hyper viscosity and related symptoms. The transient IgM increase usually returned to at least baseline level within 4 months.

Cardiovascular adverse reactions

During monotherapy with rituximab, as contained in Rituximab Equity, cardiovascular reactions 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 Equity 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 Equity compared to < 1 % on observation. In studies evaluating Rituximab Equity 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 (6,9 %) as compared to the CHOP group (1,5 %). All of these dysrhythmias either occurred in the context of a Rituximab Equity 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), 2 % of patients 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, 1,5 % of patients 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

Equity for treatment of non-Hodgkin's lymphoma. In the majority of these cases, Rituximab Equity was administered with chemotherapy.

IgG levels

During maintenance treatment with Rituximab Equity 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 Equity groups. In the observation group, the median IgG level subsequently increased to above the LLN, but remained constant in the Rituximab Equity group. The proportion of patients with IgG levels below the LLN was about 60 % in the Rituximab Equity 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 Equity 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 less frequently.

Patient subpopulations - Rituximab Equity 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 Equity was similar to the percentage of patients reporting ADRs upon initial exposure (any grade and grade 3/4 ADRs).

Patient subpopulations - Rituximab Equity 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 paediatric Diffuse Large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL)/Burkitt leukaemia (mature B-cell acute leukaemia) (BAL) and Burkitt-like lymphoma (BLL)

Summary of safety profile

A study of Lymphome Malin B chemotherapy (LMB) with or without rituximab, as contained in Rituximab Equity, was conducted in paediatric patients (aged ≥ 6 months to < 18 years old) with previously untreated advanced stage CD20 positive DLBCL/BL/BAL/BLL. Paediatric patients were administered rituximab at a dose of 375 mg/m^2 BSA and received a total of six IV infusions of rituximab (two during each of the two induction courses and one during each of the two consolidation courses of the LMB scheme).

The safety profile of rituximab, as contained in Rituximab Equity, in paediatric patients (aged ≥ 6 months to < 18 years old) with previously untreated advanced stage CD20 positive DLBCL/BL/BAL/BLL was generally consistent in type, nature and severity with the known safety profile in adult NHL and CLL patients. Addition of rituximab to chemotherapy did result in an increased risk of some events including infections (including sepsis) compared to chemotherapy only.

Rituximab Equity is not indicated for the use in paediatric population. See section 4.2 Posology and method of administration, *Special populations*.

Experience from rheumatoid arthritis

Summary of the safety profile

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

The safety profile of Rituximab Equity 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, as contained in Rituximab Equity (see section 4.4).

Patients received 2 x 1 000 mg of Rituximab Equity, separated by an interval of two weeks; in addition to methotrexate (10-25 mg/week). Rituximab infusions were administered after an intravenous infusion of 100 mg methylprednisolone; patients also received treatment with oral prednisone for 15 days.

Tabulated list of adverse reactions

Adverse reactions are listed in Table 2.

The most frequent adverse reactions considered due to receipt of Rituximab Equity were IRRs. The overall incidence of IRRs in clinical trials was 23 % with the first infusion and decreased with subsequent infusions. Serious IRRs were less frequent (0,5 % of patients) and were predominantly seen during the initial course. In addition to adverse reactions seen in RA clinical trials for rituximab, as contained in Rituximab Equity,

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

Table 2 Summary of adverse reactions reported in clinical trials or during post-marketing surveillance occurring in patients with rheumatoid arthritis receiving Rituximab Equity

System organ class	Frequent	Less frequent	Not known
Infections and Infestations	Upper respiratory tract infection, urinary tract infections, bronchitis, sinusitis, gastroenteritis, tinea pedis	PML, reactivation of hepatitis B	Serious viral infection[1], enteroviral meningoencephalitis[2]
Blood and lymphatic system disorders	Neutropenia[3]	Late neutropenia[4], serum sickness-like reaction	
Immune system disorders	[5] infusion related reactions (hypertension, nausea, rash, pyrexia, pruritus, urticaria, throat irritation, hot flush, hypotension, rhinitis, rigors, tachycardia, fatigue, oropharyngeal pain, peripheral oedema, erythema)	[5] infusion related reactions (generalised oedema, bronchospasm, wheezing, laryngeal oedema, angioneurotic oedema, generalised pruritis, anaphylaxis, anaphylactoid reaction)	
General disorders and administration site conditions			
Metabolism and nutritional disorders	Hypercholesterolaemia		
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[7]	
Musculoskeletal and connective tissue disorders	Arthralgia / musculoskeletal pain, osteoarthritis, bursitis		
Investigations	Decreased IgM levels[6], decreased IgG levels[9]		

[1] See also section infections below.

[2] Observed during post-marketing surveillance.

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

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

[5] 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.

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

[7] 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 Equity exposure was highest during the first 6 months and declined thereafter. This is mostly accounted for by IRRs (most frequent during the first treatment course), RA exacerbation and infections all of which were more frequent in the first 6 months of treatment.

Description of selected adverse reactions

Infusion-related reactions

The most frequent ADRs following receipt of Rituximab Equity in clinical studies were IRRs (refer to Table 2). Among the patients treated with rituximab, as contained in Rituximab Equity, 36 % experienced at least one IRR with 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 % 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 less frequent 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 Equity 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 Equity. 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 Equity 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 Equity. Lower respiratory tract infections (including pneumonia) have been reported during clinical trials, at a similar incidence in the Rituximab Equity-arms compared to control arms. In addition to the ADRs listed, medically serious events reported also include pneumonia at a frequency of 1,9 %.

In the post marketing setting, serious viral infections have been reported in RA patients treated with Rituximab Equity.

Cases of progressive multifocal leukoencephalopathy with fatal outcome have been reported following use of Rituximab Equity 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 Equity 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 reported less frequently in rheumatoid arthritis patients receiving Rituximab Equity (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 Equity 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 Equity treatment, the majority of which were transient and mild or moderate in severity. Neutropenia can occur several months after the administration of Rituximab Equity (see section 4.4).

In clinical trials, 0,94 % of Rituximab Equity treated patients and 0,27 % of placebo-treated patients developed severe neutropenia.

Neutropenic events, including severe late onset and persistent neutropenia, have less frequently been 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 less frequently been reported.

Laboratory abnormalities

Hypogammaglobulinaemia (IgG or IgM below the lower limit of normal) has been observed in RA patients

treated with Rituximab Equity. 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 Equity 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 Equity, 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 (GPA) and microscopic polyangiitis (MPA)

Adult induction of remission

In a GPA/MPA clinical study, 99 adult patients were treated for induction of remission of GPA and MPA with rituximab, as contained in Rituximab Equity (375 mg/m^2, once weekly for 4 weeks) and glucocorticoids.

The ADRs listed in Table 3 were all adverse events which occurred at an incidence of ≥ 5 % in the Rituximab Equity group and at a higher frequency than the comparator group.

Table 3 Adverse reactions occurring at 6-months in ≥ 5 % of patients receiving Rituximab Equity in GPA/MPA study (at a higher frequency than the comparator group), or during post-marketing surveillance.

MedDRA System Organ Class **Adverse reaction**	**Frequency**
Infections and infestations	
Urinary tract infection	7 %
Bronchitis	5 %
Herpes zoster	5 %
Nasopharyngitis	5 %

Serious vial infection[1, 2]	not known
Enteroviral meningoencephalitis[1]	not known
Blood and lymphatic system disorder	
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 %

[1] Observed during post-marketing surveillance.

[2] See also section infections below.

Adult maintenance treatment

In a GPA/MPA maintenance treatment study, a total of 57 adult patients with severe, active GPA and MPA were treated with rituximab, as contained in Rituximab Equity, for the maintenance of remission.

Table 4 Adverse reactions occurring in ≥ 5 % of patients receiving Rituximab Equity in GPA/MPA study, at a higher frequency than the comparator group, or during post-marketing surveillance.

MedDRA System organ class **Adverse reaction**	**Frequency**
Infections and infestations	
Bronchitis	14 %
Rhinitis	5 %
Serious vial infection[1, 2]	not known

Enteroviral meningoencephalitis[1]	not known
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[3]	12 %

[1] Observed during post-marketing surveillance.

[2] See also section infections below.

[3] Details on infusion-related reactions are provided in the description of selected adverse reactions section.

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

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

Long-term follow-up

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

Paediatric population

A study was conducted in 25 paediatric patients with severe, active GPA or MPA. The overall study period consisted of a 6-month remission induction phase with a minimum 18-month follow-up, up to 4,5 years overall. During the follow-up phase, rituximab, as contained in Rituximab Equity, was given at the discretion of the investigator (17 out of 25 patients received additional rituximab treatment). Concomitant treatment with other immunosuppressive therapy was permitted.

ADRs were considered as adverse events that occurred at an incidence of ≥ 10 %. These included: infections (68 % patient in the remission induction phase; 92 % patients in the overall study period), IRRs (60 % patients in the remission induction phase; 68 % patients in the overall study period), and nausea (16 % patients in the remission induction phase; 20 % patients in the overall study period).

During the overall study period, the safety profile of rituximab was consistent with that reported during the remission induction phase.

The safety profile of rituximab, as contained in Rituximab Equity, in paediatric GPA or MPA patients was consistent in type, nature and severity with the known safety profile in adult patients in the approved autoimmune indications, including adult GPA or MPA.
Rituximab Equity is not indicated for the use in paediatric population. See section 4.2 Posology and method of administration, *Special populations*.

Description of selected adverse medicine reactions

Infusion-related reactions

In the GPA/MPA adult induction of remission study, IRRs were defined as any adverse event occurring within 24 hours of an infusion and considered to be infusion-related by investigators in the safety population. Of the 99 patients treated with rituximab, as contained in Rituximab Equity, 12 % experienced at least one IRR. All

IRRs were CTC Grade 1 or 2. The most frequent IRRs included cytokine release syndrome, flushing, throat irritation, and tremor. Rituximab Equity was given in combination with intravenous glucocorticoids which may reduce the incidence and severity of these events.

In the GPA/MPA adult maintenance study, 12 % patients in the Rituximab Equity 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.

In the clinical trial in paediatric patients with GPA or MPA, the reported IRRs were predominantly seen with the first infusion (32 %), and then decreased over time with the number of Rituximab Equity infusions (20 % with the second infusion, 12 % with the third infusion and 8 % with the fourth infusion). The most common IRR symptoms reported during the remission induction phase were: headache, rash, rhinorrhoea and pyrexia (8 %, for each symptom). The observed symptoms of IRRs were similar to those known in adult GPA or MPA patients treated with Rituximab Equity. The majority of IRRs were Grade 1 and Grade 2, there were two non-serious Grade 3 IRRs, and no Grade 4 or 5 IRRs reported. One serious Grade 2 IRR (generalized oedema which resolved with treatment) was reported in one patient.
Rituximab Equity is not indicated for the use in paediatric population. See section 4.2 Posology and method of administration, *Special populations*.

Infections

In GPA/MPA induction of remission study, 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 Equity group was pneumonia at a frequency of 4 %.

In GPA/MPA maintenance study, 53 % patients in the Rituximab Equity arm experienced infections. The incidence of all grade infections was similar between the arms. Infections were predominately mild to moderate. The most frequent infections in the Rituximab Equity arm included upper respiratory tract infections, gastroenteritis, urinary tract infections and herpes zoster. The incidence of serious infections was similar in both arms (approximately 12 %). The most frequently reported serious infection in the Rituximab Equity group was mild or moderate bronchitis.

In the clinical trial in paediatric patients with severe, active GPA and MPA, 91 % of reported infections were non-serious and 90 % were mild to moderate.

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

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

Malignancies

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

In the paediatric clinical trial, no malignancies were reported with a follow-up period of up to 54 months.

Cardiovascular adverse reactions

In GPA/MPA induction of remission study, 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 induction study in the post-marketing setting.

Hypogammaglobulinaemia

Hypogammaglobulinaemia (IgA, IgG or IgM below the lower limit of normal) has been observed in adult and paediatric GPA and MPA patients treated with Rituximab Equity.

In the GPA/MPA induction of remission study, at 6 months, in the Rituximab Equity group, 27 %, 58 % and 51 % of patients with normal immunoglobulin levels at baseline had low IgA, IgG and IgM levels, respectively. The rate of overall infections and serious infections was not increased after the development of low IgA, IgG or IgM.

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

In the paediatric clinical trial, during the overall study period, 12 % patients reported an event of hypogammaglobulinaemia, 72 % had prolonged (defined as Ig levels below lower limit of normal for at least 4 months) low IgG levels (of whom 15 patients also had prolonged low IgM).

Three patients received treatment with intravenous immunoglobulin (IV-IG). Based on limited data, no firm conclusions can be drawn regarding whether prolonged low IgG and IgM led to an increased risk of serious infection in these patients. The consequences of long term B-cell depletion in paediatric patients are unknown. Rituximab Equity is not indicated for the use in paediatric population. See section 4.2 Posology and method of administration, *Special populations*.

Neutropenia

In the GPA/MPA induction of remission study, 24 % of patients in the Rituximab Equity 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 Equity-treated patients.

In the GPA/MPA maintenance study, the incidence of all-grade neutropenia was 0 % for Rituximab Equity 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 less frequently.

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. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Limited experience with doses higher than the approved dose of intravenous Rituximab Equity is available. The highest intravenous dose of rituximab, as contained in Rituximab Equity, 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. Consideration should be given to the need for regular monitoring of blood cell count and for increased risk of infections while patients are B-cell depleted.

In the post-marketing setting five cases of rituximab (as contained in Rituximab Equity) 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

A. 30.1 Biologicals - Antibodies

Pharmacotherapeutic group: antineoplastic agents, monoclonal antibodies, ATC code: L01FA01.

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

CD20 is found on both normal and malignant B-cells, but not on haematopoietic stem cells, pro-B-cells, normal plasma cells or other normal tissue. This antigen does not internalize 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.

Rituximab binds to the CD20 antigen on B lymphocytes and initiates immunologic reactions that mediate B-cell lysis. Possible mechanism of cell lysis, include complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC). Finally, in-vitro studies have demonstrated that rituximab sensitises drug-resistant human B-cell lymphoma lines to the cytotoxic effects of some chemotherapeutic agents.

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, the duration of peripheral B-cell depletion was variable. The majority of patients received further treatment prior to B-cell repletion. Some patients experienced prolonged B-cell depletion.
In patients with granulomatosis with polyangiitis or microscopic polyangiitis, the number of peripheral blood B-cells decreased to < 10 cells/µL after two weekly infusions of rituximab 375 mg/m^2, and remained at that level in most patients up to the 6 month time point.

Of patients evaluated for human anti-mouse antibody (HAMA), none were positive. Of the patients evaluated for human anti-chimeric antibodies (HACA), 1,1 % were positive.

5.2 Pharmacokinetic properties

Non-Hodgkin's lymphoma

Based on a population pharmacokinetic analysis in NHL patients who received single or multiple infusions of rituximab as a single medicine or in combination with CHOP therapy, the typical population estimates of nonspecific clearance (CL_1), specific clearance (CL_2) likely contributed by B-cells or tumour burden, and central compartment volume of distribution (V_1) were 0,14 L/day, 0,59 L/day, and 2,7 L, respectively. The estimated median terminal elimination half-life of rituximab was 22 days (range, 6,1 to 52 days).

Baseline CD19-positive cell counts and size of measurable tumour lesions contributed to some of the variability in CL_2 of rituximab given 375 mg/m^2 as an intravenous infusion for 4 weekly doses. Patients with higher CD19-positive cell counts or tumour lesions had a higher CL_2. However, a large component of inter-individual variability remained for CL_2 after correction for CD19-positive cell counts and tumour lesion size. V_1 varied by BSA and CHOP therapy. This variability in V_1 (27,1 % and 19,0 %) contributed by the range in BSA (1,53 to 2,32 m^2) and concurrent CHOP therapy, respectively, were relatively small. Age, gender and WHO performance status had no effect on the pharmacokinetics of rituximab. Thus, 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 patients with NHL naive to rituximab, yielded a mean C_{max} following the fourth infusion of 486 µg/mL (range, 77,5 to 996,6 µg/mL). Rituximab was detectable in the serum of patients 3 to 6 months after completion of last treatment.

Upon administration of rituximab at a dose of 375 mg/m^2 as an intravenous infusion at weekly intervals for 8

doses to patients with NHL, the mean C_{max} increased with each successive infusion, spanning from a mean of 243 μg/mL (range, 16 – 582 μg/mL) after the first infusion to 550 μg/mL (range, 171 – 1177 μg/mL) after the eighth infusion.

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

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} was 408 μg/mL (range, 97 – 764 μg/mL) after the fifth 500 mg/m^2 infusion and the mean terminal half-life was 32 days (range, 14 – 62 days).

Rheumatoid arthritis

Following two intravenous infusions of rituximab at a dose of 1 000 mg, two weeks apart, the mean terminal half-life was 20,8 days (range, 8,58 to 35,9 days), mean systemic clearance was 0,23 L/day (range, 0,091 to 0,67 L/day), and mean steady-state distribution volume was 4,6 L (range, 1,7 to 7,51 L). Population pharmacokinetic analysis of the same data gave similar mean values for systemic clearance and half-life, 0,26 L/day and 20,4 days, respectively. Population pharmacokinetic analysis revealed that BSA and gender were the most significant covariates to explain inter-individual variability in pharmacokinetic parameters. After adjusting for BSA, male subjects had a larger volume of distribution and a faster clearance than female subjects. The gender-related pharmacokinetic differences are not considered to be clinically relevant and dose adjustment is not required. No pharmacokinetic data are available in patients with hepatic or renal impairment.

The pharmacokinetics of rituximab were assessed following two intravenous (IV) doses of 500 mg and 1 000 mg on Days 1 and 15. 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 x 1 0000 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 μg/mL and a mean terminal half-life of 19,2 days.

Rituximab has been shown to reduce the rate of progression of joint damage as measured by X-ray, to improve physical function and to induce major clinical response, when given in combination with methotrexate. The best responses to rituximab are seen in those who have a positive blood test to rheumatoid factor (RF) and/or anti-Cyclic Citrullinated Peptide (anti-CCP). Both tests are commonly positive in rheumatoid arthritis and aid in confirming the diagnosis.

Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA)

Based on the population pharmacokinetic analysis of data in GPA and MPA patients 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.

5.3 Preclinical safety data

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

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

Standard tests to investigate mutagenicity have not been carried out, since such tests are not relevant for this molecule. No long-term animal studies have been performed to establish the carcinogenic potential of rituximab.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate dihydrate

Polysorbate 80

Sodium chloride

Hydrochloric acid

Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial

30 months.

Diluted product

The prepared infusion solution is physically and chemically stable for 48 hours at 2-8 °C and for 24 hours at 25 °C.

From a microbiological point of view, the product 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 to 8 ºC, unless reconstitution / dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2 ºC - 8 °C).

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

Do not freeze.

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

6.5 Nature and contents of container

Rituximab 100 Equity:

Clear Type I glass vial sealed with a grey bromobutyl rubber stopper crimped with aluminium seal with grey plastic flip-off cap. Pack of 2 vials.

Rituximab 500 Equity:

Clear Type I glass vial sealed with a grey bromobutyl stopper crimped with aluminium seal with grey plastic flip-off cap. Pack of 1 vial.

6.6 Special precautions for disposal and other handling

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

Use sterile needle and syringe to prepare Rituximab Equity. Withdraw the required amount of Rituximab Equity under aseptic conditions and dilute to a calculated rituximab concentration of 1 to 4 mg/mL in an infusion bag containing sterile, non-pyrogenic 0,9 % normal saline solution or 5 % dextrose solution (D5W) for infusion. To mix the solution, gently invert the bag to avoid foaming. Care must be taken to ensure the sterility of prepared solutions. Since the medicine does not contain any antimicrobial preservative or bacteriostatic medicines, aseptic technique must be observed.

Parenteral medicines should be inspected visually for particulate matter or discolouration prior to administration.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER(S)

RITUXIMAB 100 EQUITY: 56/30.1/0484

RITUXIMAB 500 EQUITY: 56/30.1/0485

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 03 June 2025

10. DATE OF REVISION OF THE TEXT

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