SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

MabThera® 100 Infusion (Parenteral)

MabThera® 500 Infusion (Parenteral)

WARNING

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 WARNINGS AND SPECIAL PRECAUTIONS.

COMPOSITION

Single dose vials containing 100 mg (in 10 mℓ) or 500 mg (in 50 mℓ) of rituximab concentrate solution for infusion.

Excipients: Hydrochloric acid, polysorbate 80, sodium chloride, sodium citrate, sodium hydroxide, water for injections

PHARMACOLOGICAL CLASSIFICATION

A26 Cytostatic Agents.

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Rituximab is a chimeric mouse/human monoclonal antibody that binds specifically to the trans-membrane antigen CD20. This antigen is located on pre-B and mature B lymphocytes but not on haemopoietic stem cells, pro-B cells, normal plasma cells or other normal tissue. The antigen is expressed on > 95 % of all B-cell non-Hodgkin's lymphomas (NHLs). Following antibody binding, CD20 is not internalised or shed from the cell membrane into the environment. 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 to levels below normal following the first dose of MabThera. In patients treated for haematological malignancies B-cell recovery began within 6 months of treatment and generally returning to normal levels within 12 months after completion of therapy, although in some patients this may take longer. In patients with rheumatoid arthritis, 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 Granulomatosis with polyangiitis (Wegener's) (GPA) and Microscopic polyangiitis (MPA) patients, peripheral blood CD19 B-cells depleted to less than 10 cells/µℓ, following the first two infusions of rituximab and remained at that level in most patients through month 6.

Of 67 patients evaluated for human anti-mouse antibody (HAMA), none were positive. Of 356 patients evaluated for human anti-chimeric antibodies (HACA), 1,1 % (4 patients) were positive.

Pharmacokinetic properties

Elimination and distribution

Non-Hodgkin's Lymphoma

Based on a population pharmacokinetic analysis in 298 NHL patients who received single or multiple infusions of rituximab as a single agent or in combination with CHOP therapy, the typical

population estimates of non-specific clearance (CL_1), specific clearance (CL_2) likely contributed by B cells or tumor burden, and central compartment volume of distribution (V_1) were 0,14 ℓ /day, 0,59 ℓ/day, and 2,7 ℓ, respectively. The estimated median terminal elimination half-life of rituximab was 22 days (range, 6,1 to 52 days). Baseline CD19-positive cell counts and size of measurable tumour lesions contributed to some of the variability in CL_2 of rituximab in data from 161 patients given 375 mg/m^2 as an IV infusion for 4 weekly doses. Patients with higher CD19-positive cell counts or tumor lesions had a higher CL_2. However, a large component of inter-individual variability remained for CL_2 after correction for CD19-positive cell counts and tumor lesion size. V_1 varied by body surface area (BSA) and CHOP therapy. This variability in V_1 (27,1 % and 19,0 %) contributed by the range in BSA (1,53 to 2,32 m^2) and concurrent CHOP therapy, respectively, were relatively small. Age, gender, race, and WHO performance status had no effect on the pharmacokinetics of rituximab. This analysis suggests that dose adjustment of rituximab with any of the tested covariates is not expected to result in a meaningful reduction in its pharmacokinetic variability.

Rituximab at a dose of 375 mg/m^2 was administered as an IV infusion at weekly intervals for 4 doses to 203 patients with NHL naive to rituximab. The mean C_{max} following the fourth infusion was 486 µg/mℓ (range, 77,5 to 996,6 µg/mℓ). The peak and trough serum levels of rituximab were inversely correlated with baseline values for the number of circulating CD19-positive B-cells and measures of disease burden. Median steady-state serum levels were higher for responders compared with non-responders. Serum levels were higher in patients with International Working Formulation (IWF) subtypes B, C, and D as compared with those with subtype A.

Rituximab was detectable in the serum of patients 3 to 6 months after completion of last treatment.

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

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

Chronic Lymphocytic Leukaemia (CLL)

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

The pharmacokinetics of rituximab were assessed following two IV doses of 500 mg and 1 000 mg on Days 1 and 15 in four studies. In all these studies, rituximab pharmacokinetics were dose proportional over the limited dose range studied. Mean C_{max} for serum rituximab following first infusion ranged from 157 to 171 µg/mℓ for 2 x 500 mg dose and ranged from 298 to 341 µg/mℓ for 2 x 1 000 mg dose. Following second infusion, mean C_{max} ranged from 183 to 198 µg/mℓ for the 2 × 500 mg dose and ranged from 355 to 404 µg/mℓ for the 2 × 1 000 mg dose. Mean terminal elimination half-life ranged from 15 to 16,5 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 1000 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 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 MabThera 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 (Wegener's) (GPA) and Microscopic polyangiitis (MPA)

Based on the population pharmacokinetic analysis of data in 97 GPA and MPA patients who received 375 mg/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 GPA and MPA patients appear similar to what has been observed in RA patients (*see section above*).

INDICATIONS

Non-Hodgkin's Lymphoma

MabThera 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

MabThera 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

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

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

MabThera IV 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).

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients or to murine proteins.

Active, severe infections.

Patients in a severely immunocompromised state.

Severe heart failure (New York Heart Association Class IV) or severe, uncontrolled cardiac disease. See WARNINGS AND SPECIAL PRECAUTIONS and SIDE EFFECTS.

WARNINGS AND SPECIAL PRECAUTIONS

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

Infusion-related adverse events:

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

Premedication consisting of an analgesic/anti-pyretic and an anti-histaminic, should always be administered before each infusion of MabThera. For RA patients, pre-medication with glucocorticoids should also be administered before each infusion of MabThera, in order to reduce the frequency and severity of infusion-related reactions. See DOSAGE AND DIRECTIONS FOR USE, and SIDE EFFECTS.

Patients with a high number (> 25 x 10^9/ℓ) of circulating malignant cells or high tumour burden such as patients with CLL and mantle cell lymphoma may be at higher risk of especially severe infusion-related reactions. These patients 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. (See SIDE EFFECTS).

For RA patients, most infusion-related events reported in clinical trials were mild to moderate in severity. Severe infusion-related reactions with fatal outcome have been reported in the post-marketing setting (see SIDE EFFECTS*, Post-Marketing, RA section*). Closely monitor patients with pre-existing cardiac conditions and those who experienced prior cardiopulmonary adverse reactions. The most common symptoms were 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 of any treatment course than following the second infusion. Subsequent MabThera infusions were better tolerated by patients than the initial infusion. Fewer than 1 % of patients experienced serious IRRs, with most of these reported during the first infusion of the first course (see SIDE EFFECTS).

MabThera is associated in more than 77 % of patients with infusion-related reactions. These may be related to the cytokine release syndrome and/or release of chemical mediators. Severe infusion-related reactions may be clinically indistinguishable from hypersensitivity reactions or cytokine release syndrome. Severe infusion-related reactions usually manifest within 30 minutes

to 2 hours after starting the first MabThera infusion, and are characterised by *pulmonary events* and includes, in some cases, *rapid tumour lysis* and *features of tumour lysis syndrome* in addition to fever, chills, rigors. Other symptoms include flushing, angioedema, nausea, urticaria/rash, fatigue, headache, throat irritation, rhinitis, vomiting, and tumour pain. Hypotension and bronchospasm accompanied these symptoms in about 10 % of the cases.

Severe cytokine release syndrome is characterised by severe dyspnoea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema.

Fatal outcomes have been reported for patients who developed severe cytokine release syndrome, occasionally associated with signs and symptoms of tumour lysis syndrome leading to multi-organ failure, respiratory failure and renal failure.

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 DOSAGE AND DIRECTIONS FOR USE) and should receive aggressive symptomatic treatment. Since initial improvement of clinical symptoms may be followed by deterioration, these patients should be closely monitored until tumour lysis syndrome and pulmonary infiltration have been resolved or ruled out. Further treatment of patients after complete resolution of signs and symptoms has rarely resulted in repeated severe cytokine release syndrome.

Most infusion events reported were mild to moderate in severity. The proportion of affected patients decreases with subsequent infusions. Infusion reaction symptoms are usually reversible with a reduction in rate, or interruption of the infusion. Treatment of infusion-related symptoms with an antihistaminic, antipyretic and a pain reliever is recommended. Additional treatment with oxygen, bronchodilators, glucocorticoids or IV saline may be indicated. In most cases, the infusion

can be resumed at a 50 % reduction in rate (e.g. from 100 mg/h to 50 mg/h) when symptoms have completely resolved. Most patients who have experienced non-life threatening infusion-related reactions have been able to complete the full course of MabThera therapy. Further treatment of patients after complete resolution of signs and symptoms has rarely resulted in repeated severe infusion-related reactions.

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

In clinical studies 10/990 (1 %) patients with rheumatoid arthritis who received a first infusion of MabThera at any dose experienced a severe reaction during the infusion. MabThera infusions should be administered in an environment where full resuscitation facilities are immediately available, and under the close supervision of an experienced doctor.

Infusion-related reactions for GPA and MPA patients were similar to those seen for RA patients in clinical trials (*see* SIDE EFFECTS – *Granulomatosis with polyangiitis (Wegener's) and Microscopic polyangiitis*). For GPA and MPA patients, MabThera was given in combination with high doses of glucocorticoids (see DOSAGE AND DIRECTIONS FOR USE), which may reduce the incidence and severity of these events.

Regarding the management of infusion-related reactions:

- MabThera (rituximab) infusion should be discontinued in patients who develop clinically significant cardiopulmonary events and they should receive medical treatment.
- Patients with pre-existing cardiac and pulmonary conditions or those with prior clinically significant cardiopulmonary adverse events should be monitored during and after subsequent infusions of MabThera (rituximab).

See SIDE EFFECTS and WARNINGS AND SPECIAL PRECAUTIONS. In the reported cases, the following factors were more frequently associated with fatal outcomes: women, patients with pulmonary infiltrates, and patients with Chronic Lymphocytic Leukaemia (CLL) or mantle cell lymphoma.

Pulmonary events:

Severe pulmonary infusion-related events that resulted in fatal outcomes have been reported during post-marketing use. Pulmonary events have included hypoxia, lung infiltration, and acute respiratory failure. Some of these events have been preceded by severe bronchospasm and dyspnoea. In some cases, symptoms worsened over time, while in others initial improvement was followed by clinical deterioration. Therefore, patients experiencing pulmonary events or other severe infusion-related symptoms should be closely monitored until complete resolution of their symptoms occur. Patients with a history of pulmonary insufficiency or those with pulmonary tumour infiltration may be at greater risk of poor outcome and should be treated with increased caution.

Acute respiratory failure may be accompanied by events such as pulmonary interstitial infiltration or oedema, visible on a chest x-ray. The syndrome usually manifests itself within one or two hours of initiating the first infusion. Patients who experience severe pulmonary events should have their infusion interrupted immediately and should receive aggressive symptomatic treatment. Since initial improvement of clinical symptoms may be followed by deterioration, these patients should be closely monitored until the pulmonary event has resolved.

Rapid tumour lysis:

MabThera mediates the rapid lysis of benign and malignant CD20-positive cells. Signs and symptoms (e.g., hyperuricaemia, hyperkalaemia, hypocalcaemia, hyperphosphataemia, acute renal failure, elevated LDH) consistent with tumour lysis syndrome (TLS) have been reported to occur within 30 minutes to 2 hours after the first MabThera infusion in patients with high numbers of circulating malignant lymphocytes. If these signs and symptoms develop, treatment should be stopped immediately. Prophylaxis for TLS should be considered for patients at risk of developing rapid tumour lysis (e.g. patients with a high tumour burden or with a high number ($> 25 \times 10^9/\ell$) of circulating malignant cells such as patients with CLL or mantle cell lymphoma). Patients at risk of developing rapid tumour lysis should be followed closely and appropriate laboratory monitoring performed. Appropriate medical therapy should be provided for patients who develop signs and symptoms consistent with rapid tumour lysis. Following treatment for and complete resolution of signs and symptoms, subsequent MabThera therapy has been administered in conjunction with prophylactic therapy for TLS in a limited number of cases.

MabThera infusions should be administered in an environment where full resuscitation facilities are immediately available, and under the close supervision of an experienced oncologist/haematologist.

Cardiovascular:

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

There are no data on the safety of MabThera in patients with moderate heart failure (NYHA class III) or severe, uncontrolled cardiovascular disease.

Angina pectoris or cardiac dysrhythmia, such as atrial flutter and fibrillation, heart failure or myocardial infarction have occurred in patients treated with MabThera. Less frequently, patients experienced an exacerbation of pre-existing cardiac conditions such as angina pectoris or congestive heart failure.

Therefore, in patients with a known cardiac history, the risk of cardiovascular complications resulting from infusion reactions should be considered before treatment with MabThera and patients should be closely monitored.

Hypersensitivity 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. Medications 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 MabThera. Clinical manifestations of anaphylaxis may appear similar to clinical manifestations of the cytokine release syndrome. Reactions attributed to hypersensitivity have been reported less frequently than those attributed to cytokine release.

Monitoring of blood counts:

Although MabThera is not myelosuppressive in monotherapy, caution should be exercised when considering treatment of patients with neutrophil counts of < 1,5 x 10^9/ℓ and/or platelet counts of < 75 x 10^9/ℓ, as clinical experience with such patients is limited. MabThera has been used in

patients who underwent autologous bone marrow transplantation and in other risk groups with a presumable reduced bone marrow function without inducing myelotoxicity.

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

Infections

Based on the mechanism of action of MabThera and the knowledge that B-cells play an important role in maintaining normal immune response, patients may have an increased risk of infection following MabThera therapy.

Serious infections, including fatalities, can occur during therapy with MabThera. MabThera treatment should not be administered to patients with active, severe infection (e.g. tuberculosis, sepsis and opportunistic infections, see CONTRAINDICATIONS), 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 MabThera in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection (see SIDE EFFECTS).

Patients treated with MabThera should avoid exposure to patients with tuberculosis and should avoid contact with children and adults recently vaccinated with attenuated live vaccines.

Patients who develop infection following MabThera therapy should be promptly evaluated and treated appropriately. It is recommended that immunoglobulin levels are determined prior to initiating treatment with MabThera.

Hepatitis B Infections:

In patients with non-Hodgkin's Lymphoma, CLL, RA, GPA and MPA receiving rituximab in combination with cytotoxic chemotherapy, cases of hepatitis B reactivation have been reported, including reports of fulminant hepatitis, some of which were fatal. The reports were confounded by both the underlying disease state and the cytotoxic chemotherapy.

Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with MabThera. At a 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 MabThera. Patients with positive hepatitis B serology should be monitored and managed following local medical standards to prevent hepatitis B reactivation.

Progressive Multifocal Leuko-encephalopathy (PML):

Cases of progressive multifocal leuko-encephalopathy (PML) have been reported during use of MabThera in NHL, and CLL (see SIDE EFFECTS). The majority of patients had received MabThera in combination with chemotherapy or as part of a haematopoietic stem cell transplant. Cases of fatal PML have been reported following use of MabThera for the treatment of rheumatoid arthritis and autoimmune diseases including Systemic Lupus Erythematosus (SLE) and Vasculitis. Several but not all of the reported cases had potential risk factors for PML, including the underlying disease, long term immunosuppressive therapy or chemotherapy. PML has also been reported in patients with autoimmune disease not treated with MabThera. The efficacy and safety of MabThera for the treatment of autoimmune diseases other than rheumatoid arthritis has not been established.

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

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 SIDE EFFECTS – Post marketing). In case of such an event, with a suspected relationship to MabThera, treatment should be permanently discontinued.

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

Patients treated with MabThera may receive non-live vaccinations. However, with non-live vaccines response rates may be reduced. In a non-randomised study, patients with relapsed low-grade NHL who received MabThera monotherapy when compared to healthy untreated controls, had a lower rate of response to vaccination with tetanus recall antigen (16 % vs. 81 %) and Keyhole Limpet Haemocyanin (KLH) neoantigen (4 % vs. 76 % when assessed for > 2-fold

increase in antibody titre). For CLL patients similar results are assumable considering similarities between both diseases but that has not been investigated in clinical trials.

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

For RA patients, doctors should review the patient's vaccination status and follow current immunisation guidelines prior to MabThera therapy. Vaccination should be completed at least 4 weeks prior to first administration of MabThera.

In a randomised study, patients with RA treated with MabThera 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 MabThera as compared to patients only receiving methotrexate. Should non-live vaccinations be required whilst receiving MabThera therapy, these should be completed at least 4 weeks prior to commencing the next course of MabThera.

In the overall experience of MabThera repeat treatment in RA patients over one year, 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.

Rheumatoid Arthritis (RA) & Granulomatosis with polyangiitis (Wegener's) (GPA) and Microscopic polyangiitis (MPA):

The efficacy and safety of MabThera for the treatment of autoimmune diseases other than rheumatoid arthritis and Granulomatosis with polyangiitis (Wegener's) and Microscopic polyangiitis has not been established.

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

Methotrexate (MTX) naïve RA populations

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

Concomitant/sequential use of other DMARDs

The concomitant use of MabThera and anti-rheumatic therapies other than those specified under the rheumatoid arthritis indication and directions for use is not recommended. There are limited data from clinical trials to fully assess the safety of the sequential use of other DMARDs (including TNF inhibitors and other biologics) following MabThera (see INTERACTIONS). The available data indicate that the rate of clinically relevant infection is unchanged when such therapies are used in patients previously treated with MabThera, however, patients should be closely observed for signs of infection if biologic agents and/or DMARDs are used following MabThera therapy.

Malignancy: Immunomodulatory medicines may increase the risk of malignancy. On the basis of limited experience with MabThera in rheumatoid arthritis patients (see SIDE EFFECTS) the present data do not seem to suggest any increased risk of malignancy. However, the possible risk for the development of solid tumours cannot be excluded at this time.

Effects on ability to drive and use machines

It is not known whether MabThera has an effect on the ability to drive and operate machines.

INTERACTIONS

Currently, limited data are available on possible medicine interactions with MabThera.

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

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

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

In patients with rheumatoid arthritis 283 patients received subsequent therapy with a biologic DMARD, following MabThera. In these patients the rate of clinically relevant infection while on

MabThera was 6,01 per 100 patient years compared to 4,97 per 100 patients years following treatment with the biologic DMARD.

PREGNANCY AND LACTATION

Safety in pregnancy and lactation has not been established.

Pregnancy: IgG immunoglobulins are known to cross the placental barrier.

Developmental toxicity studies performed in 12 pregnant cynomolgus monkeys revealed no evidence of embryotoxicity in utero. Newborn offspring of maternal animals exposed to MabThera were noted to have depleted B cell populations during the post natal phase. Abortion occurred in 3 and foetal death in 2 dams.

It is not known whether MabThera can cause foetal harm when administered to a pregnant woman or whether it can affect reproductive capacity. B-cell levels in human neonates following maternal exposure to MabThera have not been studied in clinical trials. There are no adequate and well-controlled data from studies in pregnant women, however transient B-cell depletion and lymphocytopenia have been reported in some infants born to mothers exposed to rituximab during pregnancy. For these reasons MabThera should not be given to a pregnant woman.

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 treatment and up to 12 months following MabThera therapy.

Lactation: Whether rituximab is excreted in human milk is not known. However, because maternal IgG is excreted in human milk, MabThera should not be given to women who are breastfeeding.

DOSAGE AND DIRECTIONS FOR USE

The prepared MabThera solution should be administered as an *IV* infusion through a dedicated line.

The prepared infusion solution must not be administered as an *IV* injection or bolus infusion.

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

MabThera is compatible with 0,9 % sodium chloride (normal saline) or 5 % dextrose (D5W) solutions for infusion.

Premedication 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 MabThera.

Premedication with glucocorticoids should be considered, particularly if MabThera is not given in combination with steroid-containing chemotherapy.

Patients should be closely monitored for the onset of cytokine release syndrome. In patients who develop evidence of severe reactions, especially severe dyspnoea, bronchospasm or hypoxia the infusion should immediately be interrupted. The patient should then be evaluated for evidence of tumour lysis syndrome including appropriate laboratory tests and, for pulmonary infiltration, with a chest X-ray. 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. See WARNINGS AND SPECIAL PRECAUTIONS.

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

Dosage adjustments during treatment

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

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

a) Initial treatment, weekly for 4 doses: The recommended dosage of MabThera used as a single agent/mono-therapy 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 MabThera 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.

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

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

f) Maintenance therapy:

Previously untreated patients after response to induction treatment with R-CHOP may receive maintenance therapy with MabThera given at 375 mg/m^2 body surface area 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 MabThera plus CVP or with FCM.

Relapsed/refractory patients after response to induction treatment may receive maintenance therapy with MabThera given at 375 mg/m^2 body surface area 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:

MabThera should be used in combination with CHOP chemotherapy (R-CHOP). The recommended dosage is 375 mg/m^2 body surface area, 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 MabThera.

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 MabThera 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 MabThera infusion (Cycle 2) can continue to receive subsequent MabThera 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 (see SIDE EFFECTS).

Chronic Lymphocytic Leukaemia (CLL):

Premedication consisting of an analgesic/anti-pyretic (*e.g. paracetamol*) and an antihistaminic (*e.g. diphenhydramine*) should always be administered before each infusion of MabThera.

Premedication with glucocorticoids should also be considered, particularly if MabThera 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 MabThera to decrease the rate and severity of acute infusion reactions and/or cytokine release syndrome.

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

Rheumatoid arthritis (RA):

Premedication consisting of an analgesic/anti-pyretic (*e.g. paracetamol*) and an antihistaminic (*e.g. diphenhydramine*) should always be administered before each infusion of MabThera.

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 MabThera infusion. See WARNINGS and SPECIAL PRECAUTIONS.

A course of MabThera consists of two 1 000 mg IV infusions. The recommended dosage of MabThera 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: The recommended initial rate for infusion is 50 mg/hr; after the first 30 minutes, it can be escalated in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.

Second infusion: Subsequent doses of MabThera IV 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):

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 MabThera.

The recommended dosage of MabThera for treatment of GPA and MPA is 375 mg/m^2 body surface area, administered as an IV infusion once weekly for 4 weeks.

Methylprednisolone 1 000 mg IV per day for 1 to 3 days is recommended in combination with MabThera 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 MabThera treatment.

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

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

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

Special Dosage Instructions:

Children and adolescents: The safety and efficacy of MabThera in children and adolescents have not been established.

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

Handling and disposal*:* Withdraw the required amount of MabThera under aseptic conditions and dilute to a calculated rituximab concentration of 1 - 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. Parenteral medications should be inspected visually for particulate matter or discolouration prior to administration.

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

SIDE EFFECTS

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

The overall safety profile of MabThera in non-Hodgkin's lymphoma and chronic lymphocytic leukaemia is based on data from patients from clinical trials and from post-marketing surveillance. These patients were treated either with MabThera 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 MabThera were infusion-related reactions 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 MabThera.

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 infusion-related reactions (including cytokine-release syndrome, tumour-lysis syndrome), infections and cardiovascular events. Other serious ADRs reported include hepatitis B reactivation and PML (See WARNINGS AND SPECIAL PRECAUTONS).

The frequencies of ADRs reported with MabThera alone or in combination with chemotherapy are summarised in the tables below. Within each frequency grouping, side effects are presented in order of decreasing seriousness. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1 000 to < 1/100) and rare (≥ 1/10 000 to < 1/1

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

MabThera monotherapy/maintenance therapy

The ADRs in Table 1, are based on data from single-arm studies including 356 patients with low-grade or follicular lymphoma, treated with MabThera weekly as single agent for the treatment or re-treatment of Non-Hodgkin’s Lymphoma. The table also contains ADRs based on data from 671 patients with follicular lymphoma who received MabThera as maintenance therapy for up to 2 years following response to initial induction with CHOP, R-CHOP, R-CVP or R-FCM). The ADRs were reported up to 12 months after treatment with monotherapy and up to 1 month after treatment with MabThera maintenance.

Table 1 ADRs reported in clinical trials or during post-marketing surveillance in patients with NHL and CLL disease treated with MabThera monotherapy/ maintenance or in combination with chemotherapy.

System Organ Class	**Very Common**	**Common**	**Un common**	**Rare**	**Very Rare**	**Not Known[8]**
Infections and infestations	bacterial infections, viral infections [+]bronchitis	sepsis, [+]pneumonia, [+]febrile infection, [+]herpes zoster, [+]respiratory tract infection, fungal infections, infections of unknown aetiology, [+]acute bronchitis, [+]sinusitis, hepatitis B[1]		serious viral infection[2], *Pneumocystis jirovecii*	PML	

Blood and lymphatic system disorders	neutropenia, leucopenia, [+]febrile neutropenia, [+]thrombocytopenia	anaemia, [+]pancytopenia, [+]granulocytopenia	coagulation disorders, aplastic anaemia, haemolytic anaemia, lymphadenopathy		transient increase in serum IgM levels[3]	late neutropenia[3]
Immune system disorders	infusion related reactions, angio edema	hyper sensitivity		anaphylaxis	tumour lysis syndrome[4], cytokine release syndrome[4], serum sickness	infusion-related acute reversible thrombo-cytopenia[4]

Metabolism and nutrition disorders		hyperglycaemia, weight decrease, peripheral oedema, face oedema, increased LDH, hypo-calcaemia				
Psychiatric disorders			depression, nervousness			
Nervous system disorders		paraesthesia, hypoaesthesia, agitation, insomnia, vasodilatation, dizziness, anxiety	dysgeusia		peripheral neuropathy, facial nerve palsy[5]	cranial neuropathy, loss of other senses[5]
Eye disorders		lacrimation disorder, conjunctivitis			severe vision loss[5]	
Ear and labyrinth disorders		tinnitus, ear pain				hearing loss[5]

Cardiac disorders		+myocardial infarction[4 and 6], dysrhythmia, +atrial fibrillation, tachycardia, +cardiac disorder	+left ventricular failure, +supraventricular tachycardia, +ventricular tachycardia, +angina, +myocardial ischaemia, brady-cardia	severe cardiac events [4 and 6]	heart failure[4 and 6]	
Vascular disorders		hypertension, orthostatic hypotension, hypotension			vasculitis (predominately cutaneous), leukocytoclastic vasculitis	

Respiratory, thoracic and mediastinal disorders		Bronchospasm[4], respiratory disease, chest pain, dyspnoea, increased cough, rhinitis	asthma, bronchiolitis obliterans, lung disorder, hypoxia	interstitial lung disease[7]	respiratory failure[4]	lung infiltration
Gastrointestinal disorders	nausea	vomiting , diarrhoea, abdominal pain, dysphagia, stomatitis, constipation, dyspepsia, anorexia, throat irritation	abdominal enlarge-ment		gastro-intestinal perforation[7]	

Skin and subc-utaneous tissue disorders	pruritus, rash, [+]alopecia	urticaria, sweating, night sweats, [+]skin disorder			severe bullous skin reactions, Stevens-Johnson Syndrome, toxic epidermal necrolysis[7] (Lyell's Syndrome)	
Musculo-skeletal, connective tissue and bone disorders		hypertonia, myalgia, arthralgia, back pain, neck pain, pain				
Renal and urinary disorders					renal failure[4]	

General disorders and administration site conditions	fever, chills, asthenia, headache	tumour pain, flushing, malaise, cold syndrome, +fatigue, +shivering, +multi-organ failure[4]	infusion site pain			
Investigations	decreased IgG levels					

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

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

[2] see also section infection below

[3] see also section haematologic adverse reactions below

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

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

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

[7] includes fatal cases

[8] Frequency not known (cannot be estimated from the available data)

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

MabThera in combination with chemotherapy in NHL and CLL

The ADRs listed in Table 2 are based on the MabThera-arm data from controlled clinical trials that occurred in addition to those seen with monotherapy/maintenance therapy and/or at a higher frequency grouping: 202 patients with diffuse large B-cell lymphoma (DLBCL) treated with R-CHOP, and from 234 and 162 patients with follicular lymphoma treated with R-CHOP or R-CVP, respectively, and from 397 previously untreated CLL patients and 274 relapsed/refractory CLL patients respectively, treated with MabThera in combination with fludarabine and cyclophosphamide (R-FC).

Table 2 Summary of severe ADRs reported in patients receiving R-CHOP in DLBCL (N = 202), R-CHOP in follicular lymphoma (N = 234), R-CVP in follicular lymphoma (N = 162), R-FC in previously untreated (N = 397) or relapsed/refractory (N = 274) chronic lymphocytic leukaemia

System Organ Class	Very Common (≥ 10 %)	Common (≥ 1 % - < 10 %)
Infections and infestations	bronchitis	acute bronchitis, sinusitis hepatitis B*
Blood and lymphatic system disorders	neutropenia[#], febrile neutropenia, thrombocytopenia	pancytopenia, granulocytopenia
Skin and subcutaneous tissue disorders	alopecia	skin disorder
General disorders and administration site conditions		fatigue, shivering

*Includes reactivation and primary infections; frequency based on R-FC regimen in relapsed/refractory CLL

Frequency count was based on only severe reactions defined in clinical trials as ≥ grade 3 NCI common toxicity criteria

Only the highest frequency observed in any trial is reported

prolonged and/or delayed onset neutropenia after completion of an R-FC course in previously untreated or relapsed/refractory CLL

The following terms have been reported as adverse events, however, were reported at a similar (*< 2 % difference between the groups*) or lower incidence in the MabThera-arms compared to control arms: Haematotoxicity, neutropenic infection, urinary tract infection, septic shock, superinfection lung, implant infection, staphylococcal septicaemia, lung infection, rhinorrheoa, pulmonary oedema, cardiac failure, sensory disturbance, venous thrombosis, mucosal inflammation nos, influenza-like illness, oedema lower limb, abnormal ejection fraction, pyrexia, general physical health deterioration, fall, multi-organ failure, venous thrombosis deep limb, positive blood culture, diabetes mellitus inadequate control.

The safety profile for MabThera in combination with other chemotherapies (e.g. MCP, CHVP-IFN) is comparable to the safety profile as described for the combination of MabThera and CVP, CHOP or FC in equivalent populations.

Further information on selected, serious adverse drug reactions

Infusion-related reactions:

Monotherapy – 4 weeks treatment

Signs and symptoms suggestive of an infusion-related reaction were reported in more than 50 % of patients in clinical trials, and occurred predominantly during the first infusion. Hypotension, fever, chills, rigors, bronchospasm, sensation of tongue or throat swelling (angioedema), dyspnoea, nausea, urticaria/rash, fatigue, headache, rhinitis, pruritus, vomiting, flushing, and pain at disease sites have occurred in association with MabThera infusion as part of an infusion-related symptom complex. Some features of tumour lysis syndrome have also been observed.

Combination Therapy (R-CVP in NHL; R-CHOP in DLBCL, R-FC in CLL)

Severe infusion-related reactions occurred in up to 12 % of all patients at the time of the first treatment cycle with MabThera in combination with chemotherapy. The incidence of infusion-related symptoms decreased substantially with subsequent infusions and is < 1 % of patients by the eighth cycle. Additional reactions reported were dyspepsia, rash, hypertension, tachycardia, features of tumour lysis syndrome. Isolated cases of myocardial infarction, atrial fibrillation, pulmonary oedema and acute reversible thrombocytopenia were also reported.

Infections:

Monotherapy 4 weeks treatment:

MabThera induced B-cell depletion in 70 % to 80 % of patients but was associated with decreased serum immunoglobulins only in a minority of patients. Bacterial, viral, fungal and unknown etiology infections irrespective of causal assessment, occurred in 30,3 % of 356 patients.

Severe infectious events (grade 3 or 4), including sepsis occurred in 3,9 % of patients.

Maintenance Treatment (NHL) up to 2 years:

Higher frequencies of infections overall, including grade 3-4 infections, were observed during MabThera treatment. There was no cumulative toxicity in terms of infections reported over the 2-year maintenance period.

Data from clinical trials included cases of fatal PML in NHL patients that occurred after disease progression and retreatment (see WARNINGS AND SPECIAL PRECAUTIONS).

Combination Therapy (R-CVP in NHL; R-CHOP in DLBCL, R-FC in CLL):

No increase in the frequency of infections or infestations was observed. The most common infections were upper respiratory tract infections which were reported for 12,3 % patients on R-CVP and 16,4 % patients receiving CVP. Serious infections were reported in 4,3 % of the patients receiving R-CVP and 4,4 % of the patients receiving CVP. No life-threatening infections were reported during this study.

In the R-CHOP study the overall incidence of grade 2 to 4 infections was 45,5 % in the R-CHOP group and 42,3 % in the CHOP group. Grade 2 to 4 fungal infections were more frequent in the R-CHOP group (4,5 % vs 2,6 % in the CHOP group); this difference was due to a higher incidence of localised Candida infections during the treatment period.

The incidence of grade 2 to 4 herpes zoster, was higher in the R-CHOP group (4,5 %) than in the CHOP group (1,5 %). The proportion of patients with grade 2 to 4 infections and/or febrile neutropenia was 55,4 % in the R-CHOP group and 51,5 % in the CHOP group. In patients with CLL, the incidence of grade 3 or 4 hepatitis B infection (reactivation and primary infection) was 2 % R-FC vs 0 % FC.

Haematologic adverse reactions:

Monotherapy 4 weeks treatment

Haematologic abnormalities occurred in a minority of patients and are usually mild and reversible. Severe (grade 3 and 4) thrombocytopenia and neutropenia were reported in 1,7 % and 4,2 % of patients respectively, and severe anaemia was reported in 1,1 % of patients.

Maintenance Treatment (NHL) up to 2 years

There was a higher incidence of grade 3-4 leucopenia (observation 2 %, MabThera 5 %) and neutropenia (observation 4 %, MabThera 10 %) in the MabThera arm compared to the observation arm. The incidence of grade 3 to 4 thrombocytopenia was low (observation 1 %, MabThera < 1 %). In approximately half of the patients with available data on B-cell recovery after the end of MabThera induction treatment, it took 12 months or more for their B-cell levels to return to normal values.

Combination Therapy (R-CVP in NHL; R-CHOP in DLBCL, R-FC in CLL)

During treatment course in studies with MabThera in combination with chemotherapy, grade 3/4 leucopenia (R-CHOP 88 % vs CHOP 79 %, R-FC 23 % vs FC 12 %), neutropenia (R-CVP 24 % vs CVP 14 %; R-CHOP 97 % vs CHOP 88 %, R-FC 30 % vs FC 19 % in previously untreated CLL), were usually reported with higher frequencies when compared to chemotherapy alone. However, the higher incidence of neutropenia in patients treated with MabThera 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 some cases neutropenia was prolonged or with a late onset following treatment in the MabThera plus FC group.

No relevant difference between the treatment arms was observed with respect to grade 3 and 4 anaemia or thrombocytopenia.

In the CLL first-line study, grade 3/4 anaemia was reported by 4 % of patients treated with R-FC compared to 7 % of patients receiving FC, and grade 3/4 thrombocytopenia was reported by 7 % of patients in the R-FC group compared to 10 % of patients in the FC group. In the relapsed/refractory CLL study, adverse events of grade 3/4 anaemia were reported in 12 % of patients treated with R-FC compared to 13 % of patients receiving FC and grade 3/4 thrombocytopenia was reported by 11 % of patients in the R-FC group compared to 9 % of patients in the FC group.

Cardiovascular events:

Monotherapy 4 weeks treatment:

Cardiovascular events were reported in 18,8 % of patients during the treatment period. The most frequently reported events were hypotension and hypertension. Cases of grade 3 or 4 dysrhythmia (including ventricular and supraventricular tachycardia) and angina pectoris during a MabThera-infusion were reported.

Maintenance Treatment (NHL) up to 2 years:

The incidence of grade 3 to 4 cardiac disorders was comparable between the two treatment groups. Cardiac events were reported as serious adverse event in < 1 % of patients on observation and in 3 % of patients on MabThera: atrial fibrillation (1 %), myocardial infarction (1 %), left ventricular failure (< 1 %), myocardial ischaemia (< 1 %).

Combination Therapy (R-CVP in NHL; R-CHOP in DLBCL, R-FC in CLL):

In the R-CHOP study 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 % of patients) as compared to the CHOP group (1,5 % of patients). All of these dysrhythmias either occurred in the context of a MabThera infusion or were associated with predisposing conditions such as fever, infection, acute myocardial infarction or pre-existing respiratory and cardiovascular disease (see WARNINGS AND SPECIAL PRECAUTIONS). 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.

IgG levels:

Maintenance Treatment (NHL) up to 2 years:

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

Neurologic events

Combination Therapy (R-CVP in NHL; R-CHOP in DLBCL, R-FC in CLL)

During the treatment period, 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).

Subpopulations

Monotherapy – 4 weeks treatment:

Elderly patients (≥ 65 years): The incidence of any adverse event and of grade 3 and 4 adverse events was similar in elderly and younger patients (88,3 % vs 92,0 % for any adverse event and 16,0 % vs 18,1 % for grade 3 and 4 adverse events).

Combination Therapy:

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

Bulky disease: Patients with bulky disease had a higher incidence of grade 3 and 4 adverse events than patients without bulky disease (25,6 % vs 15,4 %). The incidence of any adverse event was similar in these two groups (92,3 % in bulky disease vs 89,2 % in non-bulky disease).

Re-treatment with Monotherapy: The percentage of patients reporting any adverse event and grade 3 and 4 adverse events upon re-treatment with further courses of MabThera was similar to the percentage of patients reporting any adverse event and grade 3 and 4 adverse events upon initial exposure (95,0 % vs 89,7 % for any adverse event and 13,3 % vs 14,8 % for grade 3 and 4 adverse events).

Experience from Rheumatoid Arthritis Clinical Trials

The safety profile of MabThera IV in the treatment of patients with moderate to severe RA is summarised in the sections below. In the all exposure population more than 3 000 patients have received at least one treatment course and were followed for periods ranging from 6 months to over 5 years with an overall exposure equivalent to 7 198 patient years; approximately 2 300 patients received two or more courses of treatment during the follow up period.

The ADRs listed in Table 3 are based on data from placebo-controlled periods of four multicentre, RA clinical trials. The patient populations receiving MabThera differed between studies, ranging from early active RA patients who were methotrexate (MTX) naïve, through MTX inadequate responders (MTX-IR) to patients who had inadequate response to anti-TNF therapies (TNF-IR).

Patients received either 2 x 1 000 mg or 2 x 500 mg of MabThera separated by an interval of two weeks; in addition to methotrexate (10 - 25 mg/week) (see DOSAGE and DIRECTIONS FOR USE in RA). MabThera infusions were administered after an IV infusion of 100 mg methylprednisolone; the majority of patients also received treatment with oral prednisolone for 15 days; patients also received treatment with oral prednisone for 15 days. Events are listed in Table 3.

The ADR's listed in Table 3 are those which occurred at a rate of at least a 2 % difference compared to the control arm and are presented regardless of dose. Frequencies are defined as

very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100) and very rare (< 1/10 000). Within each frequency grouping, side effects are presented in order of decreasing seriousness.

The most frequent adverse reaction considered due to receipt of MabThera were -infusion-related reactions (IRRs).

The overall incidence of IRRs in clinical trials was 23 % with the first infusion and decreased with subsequent infusions. Serious IRRs were uncommon (0,5 % of patients) and were predominantly seen during the initial course. In addition to adverse reactions seen in RA clinical trials for MabThera, progressive multifocal leuko-encephalopathy (PML) and serum sickness-like reaction have been reported during post-marketing experience (see WARNINGS AND SPECIAL PRECAUTIONS).

Table 3 Summary of adverse drug reactions reported in clinical trials or during post-marketing surveillance occurring in patients with Rheumatoid Arthritis receiving MabThera

System Organ Class	Very Common	Common	Uncommon	Rare	Very rare
Infections and Infestations	Upper respiratory tract infections	Bronchitis, sinusitis, gastroenteritis, tinea pedis			PML, reactivation of hepatitis B
Blood and Lymphatic System Disorders				Late neutropenia [2]	Serum sickness-like reaction
Immune System Disorders	[3]Infusion-related reactions		[3]Infusion-related reactions		

General Disorders and Administration Site Conditions	(hypertension, nausea, rash, pyrexia, pruritis, urticaria, throat irritation, hot flushes hypotension, rhinitis, rigors, tachycardia, fatigue, oropharyngeal pain, peripheral oedema, erythema)		(generalised oedema, bronchospasm, wheezing, laryngeal oedema, angioneurotic oedema, generalised pruritis, anaphylaxis, anaphylactoid reaction)		
Metabolism and Nutritional Disorders		Hypercholesterolaemia			
Nervous System Disorders	Headache	Paraesthesia, migraine, dizziness, sciatica			

Skin and Subcutaneous Tissue Disorders		Alopecia			Toxic Epidermal Necrolysis (Lyell's Syndrome), Stevens-Johnson Syndrome[5]
Psychiatric Disorders		Depression, anxiety			
Gastro-intestinal Disorders		Dyspepsia, diarrhoea, gastro-eosophageal reflux, mouth ulceration, upper abdominal pain			
Musculoskeletal Disorders		Arthralgia / musculoskeletal pain, osteoarthritis, bursitis			
Investigations	Decrease IgM levels[4]	Decrease IgG levels[4]			

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

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

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

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

[5] Includes fatal cases

Multiple Courses

Multiple courses of treatment are associated with a similar adverse event profile to that observed following first exposure. The incidence of acute infusion reactions following subsequent treatment courses was generally lower than the incidence following the first infusion of MabThera.

The safety profile improved with subsequent courses due to a decrease in IRRs, RA exacerbation and infections, all of which were more frequent in the first 6 months of treatment.

Further information on selected adverse reactions:

Infusion-related reactions

The most frequent ADRs following receipt of MabThera in clinical studies were infusion-related reactions (IRRs) (refer to Table 3). Among the 3 189 patients treated with MabThera, 1 135 (36 %) experienced at least one IRR with 733/3 189 (23 %) of patients experiencing an IRR following first infusion of the first exposure to MabThera. The incidence of IRRs decline for all subsequent infusions. In clinical studies fewer than 1 % (17/3 189) of patients experienced a serious IRR. There were no CTC Grade 4 IRRs and no deaths due to IRRs. The proportion of CTC Grade 3 events, and of IRRs leading to withdrawal decreased by course and were rare from course 3 onwards. Pre-medication with intravenous glucocorticoid significantly reduced the incidence and severity of IRRs (see DOSAGE AND DIRECTIONS FOR USE).

Infections

The overall rate of infection was approximately 94 per 100 patient years in MabThera 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 antibiotic was approximately 4 per 100 patient years. The rate of serious infections did not show any significant increase following multiple courses of MabThera. Lower respiratory tract infections (including pneumonia) have been reported during clinical trials, at a

similar incidence in the MabThera arms compared to control arms. In addition to the ADRs in Table 3, medically serious events reported also include pneumonia at a frequency of 1,9 %.

Cases of progressive multifocal leukoencephalopathy with fatal outcome have been reported following use of MabThera 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 MabThera 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 in RA patients receiving MabThera (see WARNINGS AND SPECIAL PRECAUTIONS).

Malignancies

The incidence of malignancy following exposure to MabThera in clinical studies (0,8 per 100 patient years) lies within the range expected for an age and gender matched population.

Cardiovascular

Serious cardiac events were reported at a rate of 1,3 per 100 patients years in the MabThera treated patients compared to 1,3 per 100 patient years in placebo treated patients. The proportion of patients experiencing cardiac events (all or serious) did not increase over multiple courses.

Neutropenia

Events of neutropenia were observed with MabThera treatment. Neutropenia can occur several months after the administration of MabThera (see WARNINGS AND SPECIAL PRECAUTIONS). In placebo-controlled periods of clinical trials, 0,94 % (13/1 382) of rituximab treated patients and 0,27 % (2/731) of placebo patients developed severe neutropenia. Neutropenic events, including severe late onset and persistent neutropenia, have been reported in the post-marketing setting, some of which were associated with fatal infections.

Skin and subcutaneous tissue disorders

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

Laboratory abnormalities

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

The safety and effectiveness of MabThera 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 MabThera, in some cases severe and requiring long-term immunoglobulin substitution therapy. The consequences of long term B cell depletion in paediatric patients are unknown.

Clinical Trial Experience in Granulomatosis with polyangiitis (Wegener's) (GPA) and Microscopic polyangiitis (MPA)

In the GPA and MPA clinical study, 99 patients were treated with MabThera (375 mg/m^2, once weekly for 4 weeks) and glucocorticoids.

The ADRs listed in (Table 4) were all adverse events which occurred at an incidence of ≥ 10 % in the MabThera-treated group. These frequencies are defined as very common (≥ *1/10).*

Table 4 Incidence of Very Common (≥ 10 %) ADRs for MabThera IV-treated GPA and MPA Patients in Clinical Study up to Month 6*

Adverse reactions	MabThera n = 99	Cyclophosphamide n = 98
Infections and infestations		
Infections[a]	61 (61,6 %)	46 (46,9 %)
Gastrointestinal disorders		
Nausea	18 (18,2 %)	20 (20,4 %)
Diarrhoea	17 (17,2 %)	12 (12,2 %)
Nervous system disorders		
Headache	17 (17,2 %)	19 (19,4 %)
Musculoskeletal and connective tissue disorders		
Muscle spasm	17 (17,2 %)	15 (15,3 %)
Arthralgia	13 (13,1 %)	9 (9,2 %)

Blood and lymphatic system disorders		
Anaemia	16 (16,2 %)	20 (20,4 %)
Leucopenia	10 (10,1 %)	26 (26,5 %)
General disorders and administration site conditions		
Peripheral oedema	16 (16,2 %)	6 (6,1 %)
Fatigue	13 (13,1 %)	21 (21,4 %)
Psychiatric disorders		
Insomnia	14 (14,1 %)	12 (12,2 %)
Investigations		
Increased ALT	13 (13,1 %)	15 (15,3 %)
Respiratory, thoracic and mediastinal disorders		
Cough	13 (13,1 %)	11 (11,2 %)
Epistaxis	11 (11,1 %)	6 (6,1 %)
Dyspnoea	10 (10,1 %)	11 (11,2 %)
Vascular disorders		
Hypertension	12 (12,1 %)	5 (5,1 %)
Immune system disorders		
Infusion-related reactions[b]	12 (12,1 %)	11 (11,2 %)
Skin and subcutaneous tissue disorders		
Rash	10 (10,1 %)	17 (17,3 %)

* The study design allowed for crossover or treatment by best medical judgment, and 13 patients in each treatment group received a second therapy during the 6 month study period.

a - Most common infections in the rituximab group included upper respiratory tract infections, urinary tract infections, and herpes zoster.

b - Most common terms reported in the rituximab group included cytokine release syndrome, flushing, throat irritation, and tremor.

Table 5 summarises the cardiac events observed in > 1 % of patients treated with MabThera. The rate of serious cardiac events was 2,1 per 100 patient years (95 % CI 3-15) (see WARNINGS AND SPECIAL PRECAUTIONS).

Table 5 Incidence of Cardiac Disorders (> 1 %) for MabThera IV-treated GPA and MPA patients in Clinical Study up to Month 6*

Adverse reactions	MabThera n = 99	Cyclophosphamide n = 98
Cardiac disorders		
Tachycardia	4 (4 %)	1 (1 %)
Atrial fibrillation	3 (3 %)	0 (0 %)
Palpitations	2 (2 %)	4 (4,1 %)

Further information on selected adverse drug reactions:

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

Infections: In the 99 MabThera patients, the overall rate of infection was approximately 210 per 100 patient years (95 % CI 173-256). 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 MabThera group was pneumonia at a frequency of 4 %.

Malignancies: The incidence of malignancy in MabThera-treated patients in the clinical study was 2,05 per 100 patient years. On the basis of standardised incidence ratios, this malignancy rate appears to be similar to rates previously reported in GPA and MPA populations.

Hepatitis-B reactivation: Cases of hepatitis-B reactivation, some with fatal outcome, have been reported in Granulomatosis with polyangiitis and Microscopic polyangiitis patients receiving MabThera in the post-marketing setting.

Laboratory Abnormalities:

RA patients

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

Events of neutropenia associated with MabThera treatment, the majority of which were transient and mild or moderate in severity, were observed in clinical trials in RA patients after the first course of treatment. Neutropenia can occur several months after the administration of MabThera. In placebo-controlled periods of clinical trials, 0,94 % (13/1 382) of rituximab treated patients and 0,27 % (2/731) of placebo patients developed severe (Grade 3 or 4) neutropenia.

GPA and MPA patients:

Hypogammaglobulinaemia (IgA, IgG or IgM below the lower limit of normal) has been observed in GPA and MPA patients treated with MabThera. At 6 months, in a controlled study, 27 %, 58 % and 51 % of patients in the MabThera group, with normal immunoglobulin levels at baseline, had low IgA, IgG and IgM levels, respectively.

Neutropenia: In a study of MabThera in GPA and MPA, 24 % of patients in the MabThera group (single course) developed CTC grade 3 or greater neutropenia. The effect of multiple MabThera courses on the development of neutropenia in GPA and MPA patients has not been studied in clinical trials.

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

Post-marketing experience

Non-Hodgkin's Lymphoma (NHL) and Chronic Lymphocytic Leukaemia (CLL) Patients:

The reporting frequencies in this section (rare, very rare) are based on estimated marketed exposures and largely data derived from spontaneous reports.

As part of the continuing post-marketing surveillance of rituximab safety, the following serious adverse reactions have been observed:

Infusion-related reactions: Additional cases of severe infusion-related reactions have been reported during post-marketing use of MabThera. Fatal outcomes have been reported for patients who developed severe infusion-related reactions, including cytokine release syndrome, and/or signs and symptoms of tumour lysis syndrome leading to multi-organ failure, respiratory failure, and renal failure. Pulmonary adverse reactions including severe bronchoconstriction and rarely fatalities from respiratory failure have also been reported.

Cardiovascular system: Severe cardiac events, including heart failure and myocardial infarction have been observed, mainly in patients with prior cardiac condition and/or cardiotoxic chemotherapy and mostly associated with infusion-related reactions. Vasculitis, predominantly cutaneous, such as leukocytoclastic vasculitis, has been reported very rarely.

Respiratory system: Respiratory failure/insufficiency and lung infiltration in the context of infusion-related reactions. See WARNINGS AND SPECIAL PRECAUTIONS. In addition to pulmonary events associated with infusions, interstitial lung disease, some with fatal outcome, has been reported.

Blood and lymphatic system: Cases of infusion-related acute reversible thrombocytopenia have been reported.

Skin and appendages: Severe bullous skin reaction including some fatal cases of Toxic Epidermal Necrolysis and Stevens-Johnson Syndrome, have been reported rarely.

Nervous system: Cases of posterior reversible encephalopathy syndrome (PRES) / reversible posterior leukoencephalopathy syndrome (RPLS) have been reported. Signs and symptoms include 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.

Cases of cranial neuropathy with or without peripheral neuropathy, have been reported. Signs and symptoms of cranial neuropathy, such as severe vision loss, hearing loss, loss of other senses and facial nerve palsy, occurred at various times up to several months after completion of MabThera therapy.

General disorders and administrative site conditions: Serum sickness-like reactions have been reported.

Infections and infestations: Cases of hepatitis B reactivation have been reported, the majority of which were in subjects receiving rituximab in combination with cytotoxic chemotherapy. See WARNINGS AND SPECIAL PRECAUTIONS. Other serious viral infections, either new, reactivation or exacerbation, some of which were fatal, have been reported with rituximab treatment. The majority of patients had received rituximab in combination with chemotherapy or as part of a haematopoietic stem cell transplant. Examples of these serious viral infections are infections caused by the herpes viruses (cytomegalovirus (CMV), Varicella zoster virus and Herpes simplex virus), JC virus (progressive multifocal leuko-encephalopathy (PML) and Hepatitis C virus.

Progression of Kaposi's sarcoma has been observed in MabThera-exposed patients with pre-existing Kaposi's sarcoma. These cases occurred in non-approved indications and the majority of patients were HIV positive.

Gastro-intestinal system: Gastro-intestinal perforation, in some cases leading to death, has been observed in patients receiving rituximab in combination with chemotherapy for non-Hodgkin's lymphoma.

***Rheumatoid Arthritis (RA), Granulomatosis with polyangiitis (Wegener's) (GPA) and Microscopic polyangiitis (MPA) patients*:**

Post-marketing:

Infections and Infestations: Progressive multifocal leuko-encephalopathy (PML), and reactivation of hepatitis B infection have been reported.

General disorders and administrative site conditions: Serum sickness-like reaction has been reported. Severe infusion-related reactions some with fatal outcome have been reported.

Skin and subcutaneous tissue disorders: Toxic Epidermal Necrolysis and Stevens-Johnson Syndrome some with fatal outcome have been reported and reactivation of hepatitis B infection have been reported.

Blood and lymphatic system disorders: Neutropenic events, including severe late onset and persistent neutropenia, have been reported, some of which were associated with fatal infections.

Nervous system: Cases of posterior reversible encephalopathy syndrome (PRES) / reversible posterior leukoencephalopathy syndrome (RPLS) have been reported. Signs and symptoms include 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 hypertension, immunosuppressive therapy and other concomitant therapies.

Laboratory Abnormalities:

Non-Hodgkin's Lymphoma

Blood and lymphatic system: Cases of pancytopenia have been reported. Neutropenia: The onset of neutropenia occurred usually within four weeks after the last infusion of MabThera.

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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

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.

IDENTIFICATION

MabThera is a clear to opalescent, colourless to pale yellow liquid provided in sterile, preservative-free, non-pyrogenic, single dose vials.

PRESENTATION

MabThera 100: Packs of 2 vials. Colourless 10 ml glass vial with a laminated grey butyl stopper. A two piece crimp closure for the vial consists of a metal cap with rolled-in centre hole which is sealed with a red plastic flip-off disc.

MabThera 500: Pack of 1 vial. Colourless 50 ml glass vial with a laminated grey butyl stopper. A two piece crimp closure for the vial consists of a metal cap with rolled-in centre hole which is sealed with a grey plastic flip-off disc.

STORAGE INSTRUCTIONS

Store vials between 2 - 8 °C. Protect vials from sunlight. Do not freeze. Store in outer carton until required for use.

The diluted product is physically and chemically stable for 24 hours at 2 - 8 °C plus subsequently 12 hours at room temperature ± 25 ºC. From a microbiological point of view the diluted 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 - 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

Store out of reach of children.

REGISTRATION NUMBERS

MabThera 100: 32/26/0578

MabThera 500: 32/26/0579

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