

MabThera[®]

Rituximab



1. NAME OF THE MEDICINAL PRODUCT

MabThera 100 mg concentrate for solution for infusion
MabThera 500 mg concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

MabThera 100 mg concentrate for solution for infusion

Each mL contains 10 mg of rituximab.
Each 10 mL vial contains 100 mg of rituximab.

MabThera 500 mg concentrate for solution for infusion

Each mL contains 10 mg of rituximab.
Each 50 mL vial contains 500 mg of rituximab.

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

Excipients with known effects

Each 10 mL vial contains 2.3 mmol (52.6 mg) sodium.
Each 50 mL vial contains 11.5 mmol (263.2 mg) sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear, colourless liquid with pH of 6.2 – 6.8 and osmolality of 324 - 396 mOsmol/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indication(s)

Non-Hodgkin's Lymphoma:

MabThera is indicated for the treatment of:

- patients with relapsed or chemoresistant 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 CD20-positive diffuse large B-cell non-Hodgkin's lymphoma in combination with CHOP (*cyclophosphamide, doxorubicin, vincristine and prednisone*) chemotherapy.

Chronic Lymphocytic Leukemia (CLL):

MabThera is indicated, in combination with chemotherapy, for the treatment of patients with previously untreated and relapsed/refractory CD20-positive Chronic Lymphocytic Leukemia.

Rheumatoid Arthritis:

MabThera 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 one or more tumor necrosis factor (TNF) inhibitor therapies. MabThera has been shown to reduce the rate of progression of joint damage as measured by X-ray when given in combination with methotrexate.

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

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

4.2 Dosage and Administration

General

Substitution by any other biological medicinal product requires the consent of the prescribing physician.

It is important to check the product labels to ensure that the appropriate formulation (IV or SC) and strength is being given to the patient, as prescribed.

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

Premedication and Prophylactic Medications

All indications

Premedication consisting of an analgesic/anti-pyretic (e.g., paracetamol/acetaminophen) and an anti-histaminic drug (e.g., diphenhydramine) should always be given before each administration of MabThera.

Non-Hodgkin's lymphoma and chronic lymphocytic leukaemia

In adult patients with non-Hodgkin's lymphoma and CLL, premedication with glucocorticoids should be considered if MabThera is not given in combination with glucocorticoid-containing chemotherapy.

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

Rheumatoid arthritis, granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA)

In patients with rheumatoid arthritis, GPA or MPA, premedication with 100 mg intravenous methylprednisolone should be completed 30 minutes prior to each infusion of MabThera to decrease the incidence and severity of infusion related reactions (IRRs).

In adult patients with GPA or MPA, methylprednisolone given intravenously for 1 to 3 days at a dose of 1000 mg per day is recommended prior to the first infusion of MabThera (the last dose of methylprednisolone may be given on the same day as the first infusion of MabThera). This should be followed by oral prednisone 1 mg/kg/day (not to exceed 80 mg/day, and tapered as rapidly as possible based on clinical need) during and after the 4-week induction course of MabThera treatment.

Dosage adjustments during treatment

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

MabThera IV formulation is not intended for subcutaneous administration (see section 6.6).

Do not administer the prepared infusion solutions as an intravenous push or bolus (see section 6.6).

Intravenous Formulation Infusion Rate

First intravenous infusion

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

Subsequent intravenous infusions

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

Standard dosage

Adult Low-grade or Follicular Non-Hodgkin's Lymphoma

Intravenous Formulation

Initial treatment

- *Intravenous monotherapy*

The recommended dosage of MabThera IV used as monotherapy for adult patients is 375 mg/m² body surface area (BSA), administered as an intravenous infusion (see "*Intravenous Formulation Infusion Rate*" sub-section, above) once weekly for 4 weeks.

- *Intravenous combination therapy*

The recommended dosage of MabThera IV (R-IV) in combination with any chemotherapy is 375 mg/m² BSA per cycle for a total of:

- 8 cycles R-IV with CVP (21 days/cycle)
- 8 cycles R-IV with MCP (28 days/cycle)
- 8 cycles R-IV with CHOP (21 days/cycle); 6 cycles if a complete remission is achieved after 4 cycles
- 6 cycles R-IV with R-CHVP-Interferon (21 days/cycle)

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

Re-treatment following relapse

Patients who have responded to MabThera IV initially may receive MabThera IV at a dose of 375 mg/m² BSA, administered as an IV infusion once weekly for 4 weeks (see section 5.1).

Maintenance treatment

Previously untreated patients after response to induction treatment may receive maintenance therapy with MabThera given at 375mg/m² BSA once every 2 months until disease progression or for a maximum period of two years (12 infusions in total).

Relapsed/refractory patients after response to induction treatment may receive maintenance therapy with MabThera IV given at 375 mg/m² once every 3 months until disease progression or for a maximum period of two years (8 infusions in total).

Adult Diffuse Large B-cell Non-Hodgkin's Lymphoma

Intravenous Formulation

In patients with diffuse large B cell non-Hodgkin's lymphoma MabThera IV should be used in combination with CHOP (cyclophosphamide, doxorubicin, prednisone and vincristine) chemotherapy. The recommended dosage of MabThera is 375 mg/m² BSA, administered on day 1 of each chemotherapy cycle for 8 cycles after IV administration of the glucocorticoid component of CHOP (see "*Intravenous Formulation Infusion Rate*" sub-section, above).

Chronic Lymphocytic Leukaemia

Intravenous Formulation

The recommended dosage of MabThera IV in combination with chemotherapy for previously untreated and relapsed/refractory CLL patients is 375 mg/m² BSA administered on day 1 of the first treatment cycle followed by 500 mg/m² BSA administered on day 1 of each subsequent cycle for 6 cycles in total (see section 5.1). The chemotherapy should be given after the MabThera IV infusion (see "*Intravenous Formulation Infusion Rate*" sub-section, above).

Rheumatoid Arthritis

Intravenous Formulation Only

A course of MabThera IV consists of two 1000 mg IV infusions. The recommended dosage of MabThera is 1000 mg by IV infusion followed two weeks later by the second 1000 mg IV infusion (see "*Intravenous Formulation Infusion Rate*" sub-section, above).

The need for further courses should be evaluated 24 weeks following the previous course with retreatment given based on residual disease or disease activity returning to a level above a DAS28-ESR of 2.6 (treatment to remission) (see section 5.1). Patients may receive further courses no sooner than 16 weeks following the previous course.

Alternative 120-minute subsequent infusions with the concentration of 4 mg/mL in a 250 mL volume:

If patients did not experience a serious infusion-related adverse event with their previous infusion administered over the original administration schedule, a 120-minute infusion can be administered for subsequent infusions. Initiate at a rate of 250 mg/hour for the first 30 minutes and then 600 mg/hour for the next 90 minutes. If the 120-minute infusion is tolerated, the same alternative 120-minute infusion rate can be used when administering subsequent infusions and courses.

Patients who have clinically significant cardiovascular disease including arrhythmias or previous serious infusion reactions to any prior biologic therapy or to MabThera, should not be administered the 120-minute infusion.

Adult Patients with Granulomatosis with Polyangiitis (Wegener's) (GPA) and Microscopic Polyangiitis (MPA)

Intravenous Formulation Only

Induction of remission

The recommended dosage of MabThera for treatment of adult patients with severe active GPA and MPA is 375 mg/m² BSA, administered as an IV infusion (see "*Intravenous Formulation Infusion Rate*" sub-section, above) once weekly for 4 weeks.

Methylprednisolone given IV for 1 to 3 days at a dose of 1000 mg per day is recommended in combination with MabThera IV to treat severe vasculitis symptoms, followed by oral prednisone 1 mg/kg/day (not to exceed 80mg/day, and tapered as rapidly as possible per clinical need) during and after the 4 week induction course of MabThera IV treatment.

Pneumocystis jiroveci pneumonia (PCP) prophylaxis is recommended for adult patients with GPA/MPA during and following MabThera treatment, as appropriate according to local clinical practice guidelines.

Special Dosage Instructions

Pediatric use

The safety and efficacy of MabThera IV in children and adolescents (<18 years) have not been established.

Geriatric use

No dose adjustment is required in patients aged ≥ 65 years of age.

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 for use in rheumatoid arthritis, granulomatosis with polyangiitis and microscopic polyangiitis only (see section 4.4 regarding other cardiovascular diseases).

4.4 Special warnings and precautions for use

Traceability

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

Progressive multifocal leukoencephalopathy

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

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

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

If a patient develops PML, the dosing of MabThera 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 MabThera therapy may lead to similar stabilisation or improved outcome.

Cardiac disorders

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

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 have an increased risk of infection following MabThera therapy (see section 5.1). Serious infections, including fatalities, can occur during therapy with MabThera (see section 4.8). MabThera should not be administered to patients with an active, severe infection (e.g. tuberculosis, sepsis and opportunistic infections, see section 4.3) or severely immunocompromised patients (e.g. where levels of CD4 or CD8 are very low). Physicians should exercise caution when considering the use of MabThera 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 MabThera.

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

For information on progressive multifocal leukoencephalopathy (PML) please see PML section above.

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

Hepatitis B Infections

Cases of hepatitis B reactivation, including those with a fatal outcome, have been reported in patients receiving MabThera. The majority of these patients were also exposed to cytotoxic chemotherapy. Limited information from one study in relapsed/refractory CLL patients suggests that MabThera 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 MabThera. 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 MabThera. Patients with positive hepatitis B serology (either HBsAg or HBcAb) should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation.

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.

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 MabThera, treatment should be permanently discontinued.

Non-Hodgkin's lymphoma and chronic lymphocytic leukaemia

Infusion-related reactions

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

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

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

Severe cytokine release syndrome is characterised by severe dyspnoea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. This syndrome may be associated with some features of tumour lysis syndrome such as hyperuricaemia, hyperkalaemia, hypocalcaemia, hyperphosphataemia, acute renal failure, elevated lactate dehydrogenase (LDH) and may be associated with acute respiratory failure and death. The acute respiratory failure may be accompanied by events such as pulmonary interstitial infiltration or oedema, visible on a chest X-ray. The syndrome frequently manifests itself within one or two hours of initiating the first infusion. Patients with a history of pulmonary insufficiency or those with pulmonary tumour infiltration may be at greater risk of poor outcome and should be treated with increased caution.

Patients who develop severe cytokine release syndrome should have their infusion interrupted immediately (see section 4.2) and should receive aggressive symptomatic treatment. Since initial improvement of clinical symptoms may be followed by deterioration, these patients should be closely monitored until tumour lysis syndrome and pulmonary infiltration have been resolved or ruled out. Further treatment of patients after complete resolution of signs and symptoms has rarely resulted in repeated severe cytokine release syndrome.

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

Infusion-related adverse reactions of all kinds have been observed in 77% of patients treated with MabThera (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 MabThera infusion and administration of an anti-pyretic, an antihistaminic and occasionally oxygen, intravenous saline or bronchodilators, and glucocorticoids if required. Please see cytokine release syndrome above for severe reactions.

Anaphylactic and other hypersensitivity reactions have been reported following the intravenous administration of proteins to patients. In contrast to cytokine release syndrome, true hypersensitivity reactions typically occur within minutes after starting

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

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 MabThera administration, consideration should be given to withholding anti-hypertensive medicines 12 hours prior to the MabThera infusion.

Haematological toxicities

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

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

Immunisations

The safety of immunisation with live viral vaccines, following MabThera therapy has not been studied for NHL and CLL patients and vaccination with live virus vaccines is not recommended. Patients treated with MabThera may receive non-live vaccinations; however, with non-live vaccines response rates may be reduced. In a non-randomised study, adult 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.

Paediatric population

Only limited data are available for patients under 3 years of age. See section 5.1 for further information.

Rheumatoid arthritis, granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA)

Methotrexate (MTX) naïve populations with rheumatoid arthritis

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

Infusion-related reactions

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

Severe IRRs with fatal outcome have been reported in rheumatoid arthritis patients in the post-marketing setting. In rheumatoid arthritis most infusion-related events reported in clinical trials were mild to moderate in severity. The most common symptoms were allergic reactions like headache, pruritus, throat irritation, flushing, rash, urticaria, hypertension, and pyrexia. In general, the proportion of patients experiencing any infusion reaction was higher following the first infusion than following the second infusion of any treatment course. The incidence of IRR decreased with subsequent courses (see section 4.8). The reactions reported were usually reversible with a reduction in rate, or interruption, of MabThera 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 MabThera. In most cases, the infusion can be resumed at a 50% reduction in rate (e.g. from 100 mg/h to 50 mg/h) when symptoms have completely resolved.

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

There are no data on the safety of MabThera in patients with moderate heart failure (NYHA class III) or severe, uncontrolled cardiovascular disease. In patients treated with MabThera, 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 MabThera and patients closely monitored during administration. Since hypotension may occur during MabThera infusion, consideration should be given to withholding anti-hypertensive medications 12 hours prior to the MabThera infusion.

IRRs in patients with GPA and MPA were consistent with those seen for rheumatoid arthritis patients in clinical trials and in the post-marketing setting (see section 4.8).

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 section 4.8).

Immunisation

Physicians 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 MabThera therapy. Vaccination should be completed at least 4 weeks prior to first administration of MabThera.

The safety of immunisation with live viral vaccines following MabThera therapy has not been studied. Therefore, 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, response rates to non-live vaccines may be reduced. In a randomised trial, patients with rheumatoid arthritis 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 over one year in rheumatoid arthritis, the proportions of patients with positive antibody titres against *S. pneumoniae*, influenza, mumps, rubella, varicella and tetanus toxoid were generally similar to the proportions at baseline.

Concomitant/sequential use of other DMARDs in rheumatoid arthritis

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

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

Malignancy

Immunomodulatory drugs may increase the risk of malignancy. However, available data do not suggest an increased risk of malignancy for rituximab used in autoimmune indications beyond the malignancy risk already associated with the underlying autoimmune condition.

Excipients

This medicinal product contains 2.3 mmol (or 52.6 mg) sodium per 10 mL vial and 11.5 mmol (or 263.2 mg) sodium per 50 mL vial, equivalent to 2.6% (for 10 mL vial) and 13.2% (for 50 mL vial) of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Currently, there are limited data on possible drug 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 MabThera.

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

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

In patients with rheumatoid arthritis, 283 patients received subsequent therapy with a biologic DMARD following 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 patient years following treatment with the biologic DMARD.

4.6 Fertility, pregnancy and lactation

Contraception in males and females

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

Pregnancy

IgG immunoglobulins are known to cross the placental barrier.

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 MabThera during pregnancy. Similar effects have been observed in animal studies (see section 5.3). For these reasons MabThera should not be administered to pregnant women unless the possible benefit outweighs the potential risk.

Breast-feeding

Limited data on rituximab excretion into breast milk suggest very low rituximab concentrations in milk (relative infant dose less than 0.4%). Few cases of follow-up of breastfed infants describe normal growth and development up to 2 years. However, as these data are limited and the long-term outcomes of breastfed infants remain unknown, breast-feeding is not recommended while being treated with rituximab and optimally for 6 months following rituximab 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 MabThera on the ability to drive and use machines have been performed, although the pharmacological activity and adverse reactions reported to date suggest that MabThera 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 in adults

Summary of the safety profile

The overall safety profile of MabThera 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 MabThera monotherapy (as induction treatment or maintenance treatment following induction treatment) or in combination with chemotherapy.

The most frequently observed adverse reactions (ADRs) in patients receiving MabThera were IRRs which occurred in the majority of patients during the first infusion. The incidence of infusion-related symptoms decreases substantially with subsequent infusions and is less than 1% after eight doses of 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 frequently reported or observed serious adverse 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 adverse reactions reported include hepatitis B reactivation and PML (see section 4.4.).

Tabulated list of adverse reactions

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

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

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

MedDRA System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not known
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	enteroviral meningoencephalitis ^{2,3}
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 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} , arrhythmia, +atrial fibrillation, tachycardia, +cardiac disorder	+left ventricular failure, +supraventricular tachycardia, +ventricular tachycardia, +angina, +myocardial ischaemia, bradycardia	severe cardiac disorders ^{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		gastro-intestinal 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, 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-organ failure ⁵	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 (\geq 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. Rarely fatal cases reported

⁶ signs and symptoms of cranial neuropathy. Occurred at various times up to several months after completion of MabThera 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 MabThera 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 MabThera (containing) treatment.

Description of selected adverse reactions

Infections

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

Localised candida infections as well as Herpes zoster were reported at a higher incidence in the MabThera-containing arm of randomised studies. Severe infections were reported in about 4% of patients treated with MabThera monotherapy. Higher frequencies of infections overall, including grade 3 or 4 infections, were observed during MabThera 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 MabThera treatment. The majority of patients had received MabThera in combination with chemotherapy or as part of a haematopoietic stem cell transplant. Examples of these serious viral infections are infections caused by the herpes viruses (Cytomegalovirus, Varicella Zoster Virus and Herpes Simplex Virus), JC virus (progressive multifocal leukoencephalopathy (PML)), 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 MabThera 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 MabThera-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 MabThera 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 MabThera maintenance treatment for up to 2 years, leucopenia (5% vs. 2%, grade 3/4) and neutropenia (10% vs. 4%, grade 3/4) were reported at a higher incidence when compared to observation. The incidence of thrombocytopenia was low (<1%, grade 3/4) and was not different between treatment arms. During the treatment course in studies with 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), 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 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 up to 25% of patients treated with R-FC neutropenia was prolonged (defined as neutrophil count remaining below $1 \times 10^9/L$ between Day 24 and 42 after the last dose) or occurred with a late onset (defined as neutrophil count below $1 \times 10^9/L$ later than 42 days after last dose in patients with no previous prolonged neutropenia or who recovered prior to Day 42) following treatment with MabThera 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 MabThera 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 MabThera in patients with Waldenström's macroglobulinaemia, transient increases in serum IgM levels have been observed following treatment initiation, which may be associated with hyperviscosity and related symptoms. The transient IgM increase usually returned to at least baseline level within 4 months.

Cardiovascular adverse reactions

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

Respiratory system

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

Neurologic disorders

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

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

Gastrointestinal disorders

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

IgG levels

In the clinical trial evaluating MabThera maintenance treatment in relapsed/refractory follicular lymphoma, median IgG levels were below the lower limit of normal (LLN) (< 7 g/L) after induction treatment in both the observation and the MabThera groups. In the observation group, the median IgG level subsequently increased to above the LLN, but remained constant in the MabThera group. 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).

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.

Skin and subcutaneous tissue disorders

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

Patient subpopulations - MabThera monotherapy

Elderly (65 years and above)

The incidence of adverse reactions of all grades and grade 3/4 adverse reactions was similar in elderly patients compared to younger patients (below 65 years).

Bulky disease

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

Re-treatment

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

Patient subpopulations - MabThera combination therapy

Elderly (65 years and above)

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

Experience from rheumatoid arthritis

Summary of the safety profile

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

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

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

Tabulated list of adverse reactions

Adverse reactions are listed in Table 2. Frequencies are defined as very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1000$), very rare ($< 1/10,000$) and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The adverse reactions identified only during post marketing surveillance, and for which a frequency could not be estimated, are listed under “not known”, see footnotes.

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

MedDRA System Organ Class	Very Common	Common	Uncommon	Rare	Very rare	Not known
Infections and infestations	upper respiratory tract infection, urinary tract infections	bronchitis, sinusitis, gastroenteritis, tinea pedis			PML, reactivation of hepatitis B	serious viral infection ^{1,2} , 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,		⁵ infusion related reactions (generalized oedema,			

MedDRA System Organ Class	Very Common	Common	Uncommon	Rare	Very rare	Not known
General disorders and administration site conditions	pyrexia, pruritus, urticaria, throat irritation, hot flush, hypotension, rhinitis, rigors, tachycardia, fatigue, oropharyngeal pain, peripheral oedema, erythema)		bronchospasm, wheezing, laryngeal oedema, angioneurotic oedema, generalized pruritus, anaphylaxis, anaphylactoid reaction)			
Metabolism and nutrition disorders		hyper-cholesterolemia				
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 disorders and connective tissue disorders		arthralgia/ musculoskeletal pain, osteoarthritis, bursitis				
Investigations	decreased IgM levels ⁶	decreased IgG levels ⁶				

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 adverse reaction profile to that observed following first exposure. The rate of all adverse reactions following first MabThera 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 adverse reactions following receipt of MabThera in clinical studies were IRRs (refer to Table 3). Among the 3189 patients treated with MabThera, 1135 (36%) experienced at least one IRR with 733/3189 (23%) of patients experiencing an IRR following first infusion of the first exposure to MabThera. The incidence of IRRs declined with subsequent infusions. In clinical trials fewer than 1% (17/3189) of patients experienced a serious IRR. There were no CTC Grade 4 IRRs and no deaths due to IRRs in the clinical trials. The proportion of CTC Grade 3 events and of IRRs leading to withdrawal decreased by course and were rare from course 3 onwards. Premedication with intravenous glucocorticoid significantly reduced the incidence and severity of IRRs (see 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 MabThera 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 MabThera. 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 reported from clinical trials 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 antibiotics 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 the post marketing setting, serious viral infections have been reported in RA patients treated with rituximab.

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 very rarely reported in RA patients receiving MabThera (see section 4.4).

Cardiovascular adverse reactions

Serious cardiac reactions were reported at a rate of 1.3 per 100 patient years in the MabThera 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 MabThera treatment, the majority of which were transient and mild or moderate in severity. Neutropenia can occur several months after the administration of MabThera (see section 4.4).

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

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

Skin and subcutaneous tissue disorders

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

Laboratory abnormalities

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

A small number of spontaneous and literature cases of hypogammaglobulinaemia have been observed in paediatric patients treated with 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.

Experience from granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA)

Adult induction of remission (GPA/MPA Study 1)

In GPA/MPA Study 1, 99 adult patients were treated for induction of remission of GPA and MPA with MabThera (375 mg/m², once weekly for 4 weeks) and glucocorticoids (see section 5.1).

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

Table 3 Adverse reactions occurring at 6 months in $\geq 5\%$ of adult patients receiving MabThera in GPA/MPA Study 1 (Rituximab n=99), at a higher frequency than the comparator group, or during postmarketing surveillance

MedDRA System Organ Class	Very Common	Common	Not known
Infections and infestations		urinary tract infection, bronchitis, herpes zoster, nasopharyngitis	serious viral infection ^{1,2} , enteroviral meningoencephalitis ¹
Blood and lymphatic system disorders		thrombocytopenia	
Immune system disorders		cytokine release syndrome	
Metabolism and nutrition disorders		hyperkalaemia	
Psychiatric disorders	insomnia		
Nervous system disorders	dizziness, tremor		
Vascular disorders	hypertension	flushing	
Respiratory, thoracic and mediastinal disorders	cough, dyspnoea, epistaxis	nasal congestion	
Gastrointestinal disorders	diarrhoea	dyspepsia, constipation	
Skin and subcutaneous tissue disorders		acne	
Musculoskeletal and connective tissue disorders	muscle spasms, arthralgia, back pain	muscle weakness, musculoskeletal pain, pain in extremities	
General disorders and administration site conditions	oedema peripheral		
Investigations		decreased haemoglobin	

¹ Observed during post-marketing surveillance.
² See also section infections below.

Description of selected adverse reactions

Infusion-related reactions

In GPA/MPA Study 1 (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 MabThera, 12 (12%) experienced at least one IRR. All IRRs were CTC Grade 1 or 2. The most common IRRs included cytokine release syndrome, flushing, throat irritation, and tremor. MabThera was given in combination with intravenous glucocorticoids which may reduce the incidence and severity of these events.

Infections

In GPA/MPA Study 1, 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 MabThera group was pneumonia at a frequency of 4%.

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 (2 patients [8%]) and lower respiratory tract infection (2 patients [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.

Malignancies

In GPA/MPA Study 1, the incidence of malignancy in MabThera 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.

Cardiovascular adverse reactions

In GPA/MPA Study 1, 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 MabThera in the post-marketing setting.

Hypogammaglobulinaemia

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

In GPA/MPA Study 1, at 6 months, in the MabThera group, 27%, 58% and 51% of patients with normal immunoglobulin levels at baseline had low IgA, IgG and IgM levels, respectively, compared to 25%, 50% and 46% in the cyclophosphamide group. The rate of overall infections and serious infections was not increased after the development of low IgA, IgG or IgM.

Neutropenia

In GPA/MPA Study 1, 24% of patients in the MabThera 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 MabThera-treated patients.

Skin and subcutaneous tissue disorders

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

4.9 Overdose

Limited experience with doses higher than the approved dose of intravenous MabThera IV is available from clinical trials in humans. The highest intravenous dose of MabThera tested in humans to date is 5000 mg (2250 mg/m²), tested in a dose escalation study in patients with chronic lymphocytic leukaemia. No additional safety signals were identified.

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, monoclonal antibodies and antibody drug conjugates ATC code: L01FA01

Mechanism of action

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

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

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

Pharmacodynamic effects

Peripheral B-cell counts declined below normal following completion of the first dose of MabThera. In patients treated for haematological malignancies, B-cell recovery began within 6 months of treatment and generally returned to normal levels within 12 months after completion of therapy, although in some patients this may take longer (up to a median recovery time of 23 months post-induction therapy). In rheumatoid arthritis patients, immediate depletion of B-cells in the peripheral blood was observed following two infusions of 1000 mg MabThera separated by a 14-day interval. Peripheral blood B-cell counts begin to increase from Week 24 and evidence for repopulation is observed in the majority of patients by Week 40, whether MabThera was administered as monotherapy or in combination with methotrexate. A small proportion of patients had prolonged peripheral B-cell depletion lasting 2 years or more after their last dose of MabThera. In patients with GPA or MPA, the number of peripheral blood B-cells decreased to <10 cells/ μ L after two weekly infusions of rituximab 375 mg/m², and remained at that level in most patients up to the 6 month timepoint. The majority of patients (81%) showed signs of B-cell return, with counts >10 cells/ μ L by Month 12, increasing to 87% of patients by Month 18.

Clinical efficacy and safety

Clinical efficacy and safety non-Hodgkin's lymphoma and in chronic lymphocytic leukaemia

Follicular lymphoma

Monotherapy

Initial treatment, weekly for 4 doses

In the pivotal trial, 166 patients with relapsed or chemoresistant low-grade or follicular B-cell NHL received 375 mg/m² of MabThera as an intravenous infusion once weekly for four weeks. The overall response rate (ORR) in the intent-to-treat (ITT) population was 48 % (CI_{95%} 41% - 56%) with a 6% complete response (CR) and a 42 % partial response (PR) rate. The projected median time to progression (TTP) for responding patients was 13.0 months. In a subgroup analysis, the ORR was higher in patients with IWF B, C, and D histological subtypes as compared to IWF A subtype (58 % vs. 12%), higher in patients whose largest lesion was < 5 cm vs. > 7 cm in greatest diameter (53% vs. 38%), and higher in patients with chemosensitive relapse as compared to chemoresistant (defined as duration of response < 3 months) relapse (50% vs. 22%). ORR in patients previously treated with autologous bone marrow transplant (ABMT) was 78% versus 43% in patients with no ABMT. Neither age, sex, lymphoma grade, initial diagnosis, presence or absence of bulky disease, normal or high LDH nor presence of extranodal disease had a statistically significant effect (Fisher's exact test) on response to MabThera. A statistically significant correlation was noted between response rates and bone marrow involvement. 40% of patients with bone marrow involvement responded compared to 59% of patients with no bone marrow involvement (p=0.0186). This finding was not supported by a stepwise logistic regression analysis in which the following factors were identified as prognostic factors: histological type, bcl-2 positivity at baseline, resistance to last chemotherapy and bulky disease.

Initial treatment, weekly for 8 doses

In a multi-centre, single-arm trial, 37 patients with relapsed or chemoresistant, low grade or follicular B-cell NHL received 375 mg/m² of MabThera as intravenous infusion weekly for eight doses. The ORR was 57% (95% Confidence interval (CI); 41% – 73%; CR 14%, PR 43%) with a projected median TTP for responding patients of 19.4 months (range 5.3 to 38.9 months).

Initial treatment, bulky disease, weekly for 4 doses

In pooled data from three trials, 39 patients with relapsed or chemoresistant, bulky disease (single lesion \geq 10 cm in diameter), low grade or follicular B-cell NHL received 375 mg/m² of MabThera as intravenous infusion weekly for four doses. The ORR was 36% (CI_{95%} 21% – 51%; CR 3%, PR 33%) with a median TTP for responding patients of 9.6 months (range 4.5 to 26.8 months).

Re-treatment, weekly for 4 doses

In a multi-centre, single-arm trial, 58 patients with relapsed or chemoresistant low grade or follicular B-cell NHL, who had achieved an objective clinical response to a prior course of MabThera, were re-treated with 375 mg/m² of MabThera as intravenous infusion weekly for four doses. Three of the patients had received two courses of MabThera before enrolment and thus were given a third course in the study. Two patients were re-treated twice in the study. For the 60 re-treatments on study, the ORR was 38% (CI_{95%} 26% – 51%; 10% CR, 28% PR) with a projected median TTP for responding patients of

17.8 months (range 5.4 – 26.6). This compares favourably with the TTP achieved after the prior course of MabThera (12.4 months).

Initial treatment, in combination with chemotherapy

In an open-label randomised trial, a total of 322 previously untreated patients with follicular lymphoma were randomised to receive either CVP chemotherapy (cyclophosphamide 750 mg/m², vincristine 1.4 mg/m² up to a maximum of 2 mg on day 1, and prednisolone 40 mg/m²/day on days 1 -5) every 3 weeks for 8 cycles or MabThera 375 mg/m² in combination with CVP (R-CVP). MabThera was administered on the first day of each treatment cycle. A total of 321 patients (162 R-CVP, 159 CVP) received therapy and were analysed for efficacy. The median follow-up of patients was 53 months. R-CVP led to a significant benefit over CVP for the primary endpoint, time to treatment failure (27 months vs. 6.6 months, p < 0.0001, log-rank test). The proportion of patients with a tumour response (CR, CRu, PR) was significantly higher (p < 0.0001 Chi-Square test) in the R-CVP group (80.9%) than the CVP group (57.2%). Treatment with R-CVP significantly prolonged the time to disease progression or death compared to CVP, 33.6 months and 14.7 months, respectively (p < 0.0001, log-rank test). The median duration of response was 37.7 months in the R-CVP group and was 13.5 months in the CVP group (p < 0.0001, log-rank test).

The difference between the treatment groups with respect to overall survival showed a significant clinical difference (p=0.029, log-rank test stratified by centre): survival rates at 53 months were 80.9% for patients in the R-CVP group compared to 71.1% for patients in the CVP group.

Results from three other randomised trials using MabThera in combination with chemotherapy regimen other than CVP (CHOP, MCP, CHVP/Interferon-α) have also demonstrated significant improvements in response rates, time-dependent parameters as well as in overall survival. Key results from all four studies are summarised in Table 4.

Table 4 Summary of key results from four phase III randomised studies evaluating the benefit of MabThera with different chemotherapy regimens in follicular lymphoma

Study	Treatment, N	Median FU, months	ORR, %	CR, %	Median TTF/PFS/ EFS, months	OS rates, %
M39021	CVP, 159 R-CVP, 162	53	57 81	10 41	Median TTP: 14.7 33.6 P<0.0001	53-months 71.1 80.9 p=0.029
GLSG'00	CHOP, 205 R-CHOP, 223	18	90 96	17 20	Median TTF: 2.6 years Not reached p < 0.001	18-months 90 95 p = 0.016
OSHO-39	MCP, 96 R-MCP, 105	47	75 92	25 50	Median PFS: 28.8 Not reached p < 0.0001	48-months 74 87 p = 0.0096
FL2000	CHVP-IFN, 183 R-CHVP-IFN, 175	42	85 94	49 76	Median EFS: 36 Not reached p < 0.0001	42-months 84 91 p = 0.029

EFS – Event Free Survival

TTP – Time to progression or death

PFS – Progression-Free Survival

TTF – Time to Treatment Failure

OS rates – survival rates at the time of the analyses

Maintenance therapy

Previously untreated follicular lymphoma

In a prospective, open label, international, multi-centre, phase III trial 1193 patients with previously untreated advanced follicular lymphoma received induction therapy with R-CHOP (n=881), R-CVP (n=268) or R-FCM (n=44), according to the investigators' choice. A total of 1078 patients responded to induction therapy, of which 1018 were randomised to MabThera maintenance therapy (n=505) or observation (n=513). The two treatment groups were well balanced with regards to baseline characteristics and disease status. MabThera maintenance treatment consisted of a single infusion of MabThera at 375 mg/m² body surface area given every 2 months until disease progression or for a maximum period of two years.

The pre-specified primary analysis was conducted at a median observation time of 25 months from randomization, maintenance therapy with MabThera resulted in a clinically relevant and statistically significant improvement in the primary

endpoint of investigator assessed progression-free survival (PFS) as compared to observation in patients with previously untreated follicular lymphoma (Table 5).

Significant benefit from maintenance treatment with MabThera was also seen for the secondary endpoints event-free survival (EFS), time to next anti-lymphoma treatment (TNLT) time to next chemotherapy (TNCT) and overall response rate (ORR) in the primary analysis (Table 5).

Data from extended follow-up of patients in the study (median follow-up 9 years) confirmed the long-term benefit of MabThera maintenance therapy in terms of PFS, EFS, TNLT and TNCT (Table 5).

Table 5 Overview of efficacy results for MabThera maintenance vs. observation at the protocol-defined primary analysis and after 9 years median follow-up (final analysis)

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

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

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

MabThera maintenance treatment provided consistent benefit in all predefined subgroups tested: gender (male, female), age (< 60 years, >= 60 years), FLIPI score (<=1, 2 or >= 3), induction therapy (R-CHOP, R-CVP or R-FCM) and regardless of the quality of response to induction treatment (CR, CRu or PR). Exploratory analyses of the benefit of maintenance treatment showed a less pronounced effect in elderly patients (> 70 years of age), however sample sizes were small.

Relapsed/Refractory follicular lymphoma

In a prospective, open label, international, multi-centre, phase III trial, 465 patients with relapsed/refractory follicular lymphoma were randomised in a first step to induction therapy with either CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone; n=231) or MabThera plus CHOP (R-CHOP, n=234). The two treatment groups were well balanced with regard to baseline characteristics and disease status. A total of 334 patients achieving a complete or partial remission following induction therapy were randomised in a second step to MabThera maintenance therapy (n=167) or observation (n=167). MabThera maintenance treatment consisted of a single infusion of MabThera at 375 mg/m² body surface area given every 3 months until disease progression or for a maximum period of two years.

The final efficacy analysis included all patients randomised to both parts of the study. After a median observation time of 31 months for patients randomised to the induction phase, R-CHOP significantly improved the outcome of patients with relapsed/refractory follicular lymphoma when compared to CHOP (see Table 6).

Table 6 Induction phase: overview of efficacy results for CHOP vs. R-CHOP (31 months median observation time)

	CHOP	R-CHOP	p-value	Risk Reduction ¹⁾
Primary efficacy				
ORR ²⁾	74 %	87 %	0.0003	Na
CR ²⁾	16 %	29 %	0.0005	Na
PR ²⁾	58 %	58 %	0.9449	Na

¹⁾ Estimates were calculated by hazard ratios

²⁾ Last tumour response as assessed by the investigator. The “primary” statistical test for “response” was the trend test of CR versus PR versus non-response ($p < 0.0001$)

Abbreviations: NA, not available; ORR: overall response rate; CR: complete response; PR: partial response

For patients randomised to the maintenance phase of the trial, the median observation time was 28 months from maintenance randomisation. Maintenance treatment with MabThera led to a clinically relevant and statistically significant improvement in the primary endpoint, PFS, (time from maintenance randomisation to relapse, disease progression or death) when compared to observation alone ($p < 0.0001$ log-rank test). The median PFS was 42.2 months in the MabThera maintenance arm compared to 14.3 months in the observation arm. Using a cox regression analysis, the risk of experiencing progressive disease or death was reduced by 61% with MabThera maintenance treatment when compared to observation (95% CI; 45%-72%). Kaplan-Meier estimated progression-free rates at 12 months were 78% in the MabThera maintenance group vs. 57% in the observation group. An analysis of overall survival confirmed the significant benefit of MabThera maintenance over observation ($p=0.0039$ log-rank test). MabThera maintenance treatment reduced the risk of death by 56% (95% CI; 22%-75%).

Table 7 Maintenance phase: overview of efficacy results MabThera vs. observation (28 months median observation time)

Efficacy Parameter	Kaplan-Meier Estimate of Median Time to Event (Months)			Risk Reduction
	Observation (N = 167)	MabThera (N=167)	Log-Rank p value	
Progression-free survival (PFS)	14.3	42.2	< 0.0001	61 %
Overall survival	NR	NR	0.0039	56 %
Time to new lymphoma treatment	20.1	38.8	< 0.0001	50 %
Disease-free survival ^a	16.5	53.7	0.0003	67 %
Subgroup analysis				
PFS				
CHOP	11.6	37.5	< 0.0001	71 %
R-CHOP	22.1	51.9	0.0071	46 %
CR	14.3	52.8	0.0008	64 %
PR	14.3	37.8	< 0.0001	54 %
OS				
CHOP	NR	NR	0.0348	55 %
R-CHOP	NR	NR	0.0482	56 %

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

The benefit of MabThera maintenance treatment was confirmed in all subgroups analysed, regardless of induction regimen (CHOP or R-CHOP) or quality of response to induction treatment (CR or PR) (Table 7). MabThera maintenance treatment significantly prolonged median PFS in patients responding to CHOP induction therapy (median PFS 37.5 months vs. 11.6 months, $p < 0.0001$) as well as in those responding to R-CHOP induction (median PFS 51.9 months vs. 22.1 months, $p=0.0071$). Although subgroups were small, MabThera maintenance treatment provided a significant benefit in terms of overall survival for both patients responding to CHOP and patients responding to R-CHOP, although longer follow-up is required to confirm this observation.

In a randomised, open-label trial, a total of 399 previously untreated elderly patients (age 60 to 80 years) with diffuse large B-cell lymphoma received standard CHOP chemotherapy (cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², vincristine 1.4 mg/m² up to a maximum of 2 mg on Day 1, and prednisolone 40 mg/m²/day on days 1-5) every 3 weeks for eight cycles, or MabThera 375 mg/m² plus CHOP (R-CHOP). MabThera was administered on the first day of the treatment cycle.

The final efficacy analysis included all randomised patients (197 CHOP, 202 R-CHOP), and had a median follow-up duration of approximately 31 months. The two treatment groups were well balanced in baseline disease characteristics and disease status. The final analysis confirmed that R-CHOP treatment was associated with a clinically relevant and statistically significant improvement in the duration of event-free survival (the primary efficacy parameter; where events were death, relapse or progression of lymphoma, or institution of a new anti-lymphoma treatment) (p=0.0001). Kaplan Meier estimates of the median duration of event-free survival were 35 months in the R-CHOP arm compared to 13 months in the CHOP arm, representing a risk reduction of 41%. At 24 months, estimates for overall survival were 68.2% in the R-CHOP arm compared to 57.4% in the CHOP arm. A subsequent analysis of the duration of overall survival, carried out with a median follow-up duration of 60 months, confirmed the benefit of R-CHOP over CHOP treatment (p=0.0071), representing a risk reduction of 32%.

The analysis of all secondary parameters (response rates, progression-free survival, disease-free survival, duration of response) verified the treatment effect of R-CHOP compared to CHOP. The complete response rate after cycle 8 was 76.2% in the R-CHOP group and 62.4% in the CHOP group (p=0.0028). The risk of disease progression was reduced by 46% and the risk of relapse by 51%. In all patient subgroups (gender, age, age adjusted IPI, Ann Arbor stage, ECOG, β 2 microglobulin, LDH, albumin, B symptoms, bulky disease, extranodal sites, bone marrow involvement), the risk ratios for event-free survival and overall survival (R-CHOP compared with CHOP) were less than 0.83 and 0.95 respectively. R-CHOP was associated with improvements in outcome for both high- and low-risk patients according to age adjusted IPI.

Clinical laboratory findings

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

Chronic lymphocytic leukaemia

In two open-label randomised trials, a total of 817 previously untreated patients and 552 patients with relapsed/refractory CLL were randomised to receive either FC chemotherapy (fludarabine 25 mg/m², cyclophosphamide 250 mg/m², days 1-3) every 4 weeks for 6 cycles or MabThera in combination with FC (R-FC). MabThera was administered at a dosage of 375 mg/m² during the first cycle one day prior to chemotherapy and at a dosage of 500 mg/m² on Day 1 of each subsequent treatment cycle. Patients were excluded from the study in relapsed/refractory CLL if they had previously been treated with monoclonal antibodies or if they were refractory (defined as failure to achieve a partial remission for at least 6 months) to fludarabine or any nucleoside analogue. A total of 810 patients (403 R-FC, 407 FC) for the first-line study (Table 8a and Table 8b) and 552 patients (276 R-FC, 276 FC) for the relapsed/refractory study (Table 9) were analysed for efficacy.

In the first-line study, after a median observation time of 48.1 months, the median PFS was 55 months in the R-FC group and 33 months in the FC group (p < 0.0001, log-rank test). The analysis of overall survival showed a significant benefit of R-FC treatment over FC chemotherapy alone (p = 0.0319, log-rank test) (Table 8a). The benefit in terms of PFS was consistently observed in most patient subgroups analysed according to disease risk at baseline (i.e. Binet stages A-C) (Table 8b).

**Table 8a First-line treatment of chronic lymphocytic leukaemia
Overview of efficacy results for MabThera plus FC vs. FC alone - 48.1 months median observation time**

Efficacy Parameter	Kaplan-Meier Estimate of Median Time to Event (Months)			Risk Reduction
	FC (N = 409)	R-FC (N=408)	Log-Rank p value	
Progression-free survival (PFS)	32.8	55.3	<0.0001	45%
Overall survival	NR	NR	0.0319	27%
Event free survival	31.3	51.8	<0.0001	44%
Response rate (CR, nPR, or PR)	72.6%	85.8%	<0.0001	n.a.
CR rates	16.9%	36.0%	<0.0001	n.a.
Duration of response*	36.2	57.3	<0.0001	44%
Disease free survival (DFS)**	48.9	60.3	0.0520	31%

Time to new treatment	47.2	69.7	<0.0001	42%
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Response rate and CR rates analysed using Chi-squared Test. NR: not reached; n.a.: not applicable

*: only applicable to patients achieving a CR, nPR, PR

**: only applicable to patients achieving a CR

**Table 8b First-line treatment of chronic lymphocytic leukaemia
Hazard ratios of progression-free survival according to Binet stage (ITT) – 48.1 months median observation time**

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

CI: Confidence Interval

In the relapsed/refractory study, the median progression-free survival (primary endpoint) was 30.6 months in the R-FC group and 20.6 months in the FC group (p=0.0002, log-rank test). The benefit in terms of PFS was observed in almost all patient subgroups analysed according to disease risk at baseline. A slight but not significant improvement in overall survival was reported in the R-FC compared to the FC arm.

Table 9 Treatment of relapsed/refractory chronic lymphocytic leukaemia - overview of efficacy results for MabThera plus FC vs. FC alone (25.3 months median observation time)

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

Response rate and CR rates analysed using Chi-squared Test.

*: only applicable to patients achieving a CR, nPR, PR; NR: not reached

n.a. not applicable

**: only applicable to patients achieving a CR;

Results from other supportive studies using MabThera in combination with other chemotherapy regimens (including CHOP, FCM, PC, PCM, bendamustine and cladribine) for the treatment of previously untreated and/or relapsed/refractory CLL patients have also demonstrated high overall response rates with benefit in terms of PFS rates, albeit with modestly higher toxicity (especially myelotoxicity). These studies support the use of MabThera with any chemotherapy.

Data in approximately 180 patients pre-treated with MabThera have demonstrated clinical benefit (including CR) and are supportive for MabThera re-treatment.

Clinical efficacy and safety in rheumatoid arthritis

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

Trial 1 evaluated 517 patients that had experienced an inadequate response or intolerance to one or more TNF inhibitor therapies. Eligible patients had active rheumatoid arthritis, diagnosed according to the criteria of the American College

of Rheumatology (ACR). MabThera was administered as two IV infusions separated by an interval of 15 days. Patients received 2 x 1000 mg intravenous infusions of MabThera or placebo in combination with MTX. All patients received concomitant 60 mg oral prednisone on days 2-7 and 30 mg on days 8-14 following the first infusion. The primary endpoint was the proportion of patients who achieved an ACR20 response at Week 24. Patients were followed beyond Week 24 for long term endpoints, including radiographic assessment at 56 weeks and at 104 weeks. During this time, 81% of patients, from the original placebo group received MabThera between weeks 24 and 56, under an open label extension study protocol.

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

Disease activity outcomes

MabThera in combination with methotrexate significantly increased the proportion of patients achieving at least a 20% improvement in ACR score compared with patients treated with methotrexate alone (Table 10). Across all development studies the treatment benefit was similar in patients independent of age, gender, body surface area, race, number of prior treatments or disease status.

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

Table 10 Clinical response outcomes at primary endpoint in Trial 1 (ITT population)

	Outcome†	Placebo+MTX	MabThera+MTX (2 x 1000 mg)
Trial 1		N= 201	N= 298
	ACR20	36 (18%)	153 (51%)***
	ACR50	11 (5%)	80 (27%)***
	ACR70	3 (1%)	37 (12%)***
	EULAR Response (Good/Moderate)	44 (22%)	193 (65%)***
	Mean change in DAS	-0.34	-1.83***

† Outcome at 24 weeks

Significant difference from placebo + MTX at the primary timepoint: ***p ≤ 0.0001

Patients treated with MabThera in combination with methotrexate had a significantly greater reduction in disease activity score (DAS28) than patients treated with methotrexate alone (Table 10). Similarly, a good to moderate European League Against Rheumatism (EULAR) response was achieved by significantly more MabThera treated patients treated with MabThera and methotrexate compared to patients treated with methotrexate alone (Table 10).

Radiographic response

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

In Trial 1, conducted in patients with inadequate response or intolerance to one or more TNF inhibitor therapies, receiving MabThera in combination with methotrexate demonstrated significantly less radiographic progression than patients originally receiving methotrexate alone at 56 weeks. Of the patients originally receiving methotrexate alone, 81% received MabThera either as rescue between weeks 16-24 or in the extension trial, before Week 56. A higher proportion of patients receiving the original MabThera/MTX treatment also had no erosive progression over 56 weeks (Table 11).

Table 11 Radiographic outcomes at 1 year (mITT population)

	Placebo+MTX	MabThera+MTX 2 x 1000 mg
Trial 1	(n = 184)	(n = 273)
Mean change from baseline:		
Modified total sharp score	2.30	1.01*
Erosion score	1.32	0.60*
Joint space narrowing score	0.98	0.41**

Proportion of patients with no radiographic change	46%	53%, NS
Proportion of patients with no erosive change	52%	60%, NS

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

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

Physical function and quality of life outcomes

Significant reductions in disability index (HAQ-DI) and fatigue (FACIT-Fatigue) scores were observed in patients treated with MabThera compared to patients treated with methotrexate alone. The proportions of MabThera treated patients showing a minimal clinically important difference (MCID) in HAQ-DI (defined as an individual total score decrease of > 0.22) was also higher than among patients receiving methotrexate alone (Table 12).

Significant improvement in health-related quality of life was also demonstrated with significant improvement in both the physical health score (PHS) and mental health score (MHS) of the SF-36. Further, a significantly higher proportion of patients achieved MCIDs for these scores (Table 12).

Table 12 Physical function and quality of life outcomes at week 24 in Trial 1

Outcome†	Placebo+MTX	MabThera+MTX (2 x 1000 mg)
	n=201	n=298
Mean change in HAQ-DI	0.1	-0.4***
% HAQ-DI MCID	20%	51%
Mean change in FACIT-T	-0.5	-9.1***
	n=197	n=294
Mean Change in SF-36 PHS	0.9	5.8***
% SF-36 PHS MCID	13%	48%***
Mean change in SF-36 MHS	1.3	4.7**
% SF-36 MHS MCID	20%	38%*

† Outcome at 24 weeks

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

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

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

Efficacy outcomes in MabThera treated patients were analysed based on autoantibody status prior to commencing treatment. At Week 24, patients who were seropositive to RF and/or anti-CCP at baseline had a significantly increased probability of achieving ACR20 and 50 responses compared to seronegative patients (p=0.0312 and p=0.0096) (Table 13). These findings were replicated at Week 48, where autoantibody seropositivity also significantly increased the probability of achieving ACR70. At Week 48 seropositive patients were 2-3 times more likely to achieve ACR responses compared to seronegative patients. Seropositive patients also had a significantly greater decrease in DAS28-ESR compared to seronegative patients (Figure 1).

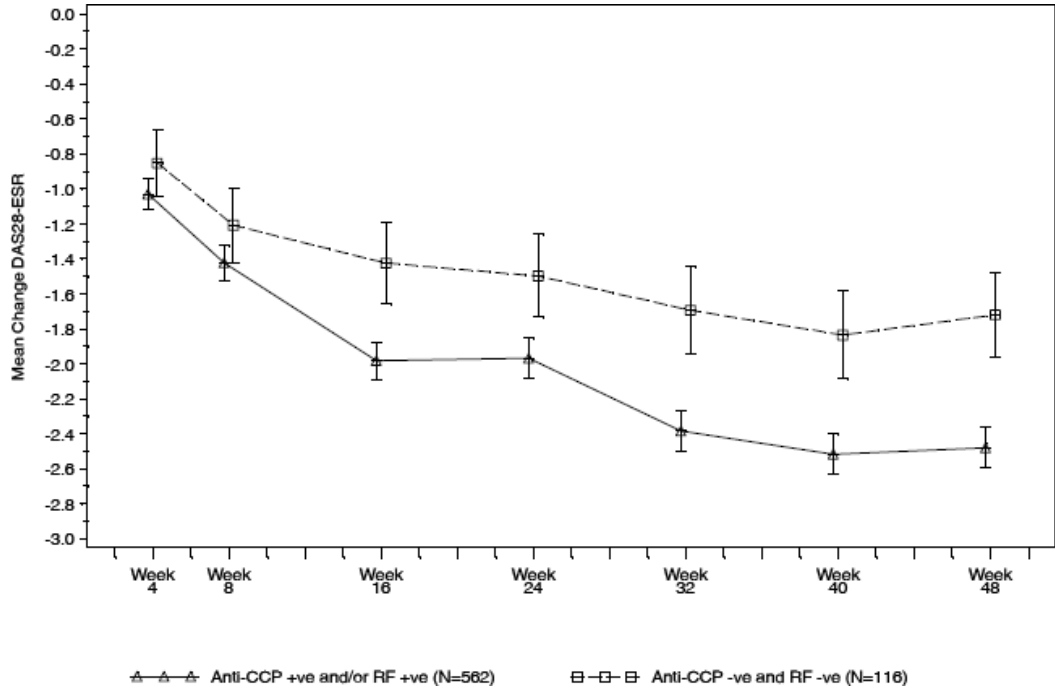
Table 13 Summary of efficacy by baseline autoantibody status

	Week 24		Week 48	
	Seropositive (n=514)	Seronegative (n=106)	Seropositive (n=506)	Seronegative (n=101)
ACR20 (%)	62.3*	50.9	71.1*	51.5
ACR50 (%)	32.7*	19.8	44.9**	22.8
ACR70 (%)	12.1	5.7	20.9*	6.9

EULAR response (%)	74.8*	62.9	84.3*	72.3
Mean change DAS28-ESR	-1.97**	-1.50	-2.48***	-1.72

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

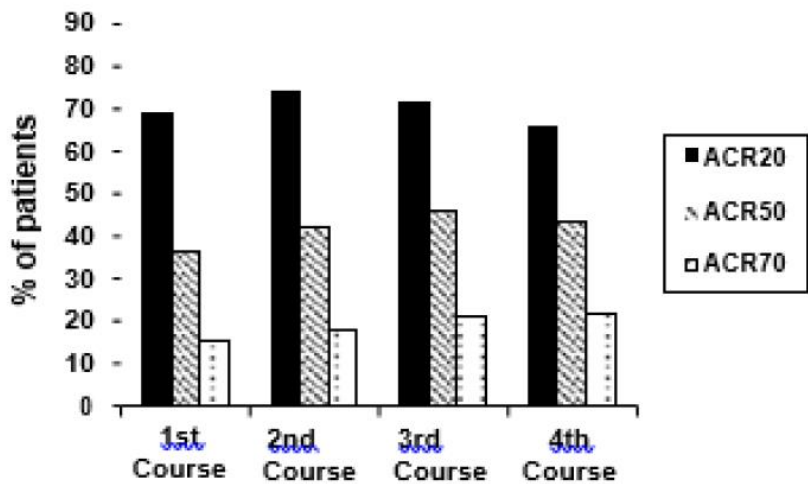
Figure 1: Change from baseline of DAS28-ESR by baseline autoantibody status



Long-term efficacy with multiple course therapy

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

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



Clinical laboratory findings

A total of 392/3095 (12.7%) patients with rheumatoid arthritis tested positive for ADA in clinical studies following therapy with MabThera. The emergence of ADA was not associated with clinical deterioration or with an increased

risk of reactions to subsequent infusions in the majority of patients. The presence of ADA may be associated with worsening of infusion or allergic reactions after the second infusion of subsequent courses.

Clinical efficacy and safety in granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA)

Adult induction of remission treatment

In GPA/MPA Study 1, a total of 197 patients aged 15 years or older with severe active GPA (75%) and MPA (24%) were enrolled and treated in an active-comparator, randomised, double-blind, multicentre, non-inferiority trial.

Patients were randomised in a 1:1 ratio to receive either oral cyclophosphamide daily (2 mg/kg/day) for 3-6 months or MabThera (375 mg/m²) once weekly for 4 weeks. All patients in the cyclophosphamide arm received azathioprine maintenance therapy in during follow-up. Patients in both arms received 1000 mg of pulse intravenous (IV) methylprednisolone (or another equivalent-dose glucocorticoid) per day for 1 to 3 days, followed by oral prednisone (1 mg/kg/day, not exceeding 80 mg/day). Prednisone tapering was to be completed by 6 months from the start of trial treatment.

The primary outcome measure was achievement of complete remission at 6 months defined as a Birmingham Vasculitis Activity Score for Wegener’s granulomatosis (BVAS/WG) of 0, and off glucocorticoid therapy. The prespecified non-inferiority margin for the treatment difference was 20%. The trial demonstrated non-inferiority of MabThera to cyclophosphamide for complete remission (CR) at 6 months (Table 14).

Efficacy was observed both for patients with newly diagnosed disease and for patients with relapsing disease (Table 15).

Table 14 Percentage of adult patients who achieved complete remission at 6 months (Intent-to-treat population*)

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

Table 15 Complete remission at 6-months by disease status

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

Worst case imputation is applied for patients with missing data

Complete remission at 12 and 18 months

In the MabThera group, 48% of patients achieved CR at 12 months, and 39% of patients achieved CR at 18 months. In patients treated with cyclophosphamide (followed by azathioprine for maintenance of complete remission), 39% of patients achieved CR at 12 months, and 33% of patients achieved CR at 18 months. From Month 12 to Month 18, 8 relapses were observed in the MabThera group compared with four in the cyclophosphamide group.

Laboratory evaluations

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

5.2 Pharmacokinetic Properties

Adult non-Hodgkin's lymphoma

Based on a population pharmacokinetic analysis in 298 NHL patients who received single or multiple infusions of MabThera as a single agent or in combination with CHOP therapy (applied MabThera doses ranged from 100 to 500 mg/m²), the typical population estimates of nonspecific clearance (CL₁), specific clearance (CL₂) likely contributed by B-cells or tumour burden, and central compartment volume of distribution (V₁) were 0.14 L/day, 0.59 L/day, and 2.7 L, respectively. The estimated median terminal elimination half-life of MabThera was 22 days (range, 6.1 to 52 days). Baseline CD19-positive cell counts and size of measurable tumour lesions contributed to some of the variability in CL₂ of MabThera in data from 161 patients given 375 mg/m² as an intravenous infusion for 4 weekly doses. Patients with higher CD19-positive cell counts or tumour lesions had a higher CL₂. However, a large component of inter-individual variability remained for CL₂ after correction for CD19-positive cell counts and tumour lesion size. V₁ varied by body surface area (BSA) and CHOP therapy. This variability in V₁ (27.1% and 19.0%) contributed by the range in BSA (1.53 to 2.32 m²) and concurrent CHOP therapy, respectively, were relatively small. Age, gender and WHO performance status had no effect on the pharmacokinetics of MabThera. This analysis suggests that dose adjustment of MabThera with any of the tested covariates is not expected to result in a meaningful reduction in its pharmacokinetic variability.

MabThera, administered as an intravenous infusion at a dose of 375 mg/m² at weekly intervals for 4 doses to 203 patients with NHL naive to MabThera, yielded a mean C_{max} following the fourth infusion of 486 µg/mL (range, 77.5 to 996.6 µg/mL). Rituximab was detectable in the serum of patients 3 – 6 months after completion of last treatment.

Upon administration of MabThera at a dose of 375 mg/m² as an intravenous infusion at weekly intervals for 8 doses to 37 patients with NHL, the mean C_{max} increased with each successive infusion, spanning from a mean of 243 µg/mL (range, 16 – 582 µg/mL) after the first infusion to 550 µg/mL (range, 171 – 1177 µg/mL) after the eighth infusion.

The pharmacokinetic profile of MabThera when administered as 6 infusions of 375 mg/m² in combination with 6 cycles of CHOP chemotherapy was similar to that seen with MabThera alone.

Chronic lymphocytic leukaemia

MabThera was administered as an intravenous infusion at a first-cycle dose of 375 mg/m² increased to 500 mg/m² 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/m² infusion and the mean terminal half-life was 32 days (range, 14 – 62 days).

Rheumatoid arthritis

Following two intravenous infusions of MabThera at a dose of 1000 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 1000 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 2x 1000 mg dose. Following second infusion, mean C_{max} ranged from 183 to 198 µg/mL for the 2 x 500 mg dose and ranged from 355 to 404 µg/mL for the 2 x 1000 mg dose. Mean terminal elimination half-life ranged from 15 to 16 days for the 2 x 500 mg dose group and 17 to 21 days for the 2 x 1000 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 1000 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 1000 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 1000 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 1000 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.

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

Adult Population

Based on the population pharmacokinetic analysis of data in 97 patients with granulomatosis with polyangiitis and microscopic polyangiitis who received 375 mg/m² MabThera 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. Maximum concentration during the first 180 days (C_{max}), minimum concentration at Day 180 (C180) and Cumulative area under the curve over 180 days (AUC180) were (median [range]) 372.6 (252.3-533.5) µg/mL, 2.1 (0-29.3) µg/mL and 10302 (3653- 21874) µg/mL*days, respectively. The PK parameters of rituximab in adult GPA and MPA patients appear similar to what has been observed in rheumatoid arthritis patients.

5.3 Preclinical safety data

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

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate
Polysorbate 80
Sodium chloride
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial

This medicine should not be used after the expiry date (EXP) shown on the pack.

Diluted medicinal product

After aseptic dilution in 0.9% aqueous saline solution:

The prepared infusion solution of MabThera in 0.9% aqueous saline solution is physically and chemically stable for 30 days at 2°C - 8°C plus an additional 24 hours at room temperature.

After aseptic dilution in 5% aqueous dextrose solution:

The prepared infusion solution of MabThera in 5% aqueous dextrose solution is physically and chemically stable for 24 hours at 2°C - 8°C plus an additional 12 hours at room temperature.

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

6.4 Special precautions for storage

Store vials at 2°C - 8°C (in a refrigerator). Keep the container in the outer carton in order to protect from light.

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

6.5 Nature and contents of container

MabThera 100 mg concentrate for solution for infusion

Clear Type I glass vials with butyl rubber stopper containing 100 mg of rituximab in 10 mL.
Pack of 2 vials.

MabThera 500 mg concentrate for solution for infusion

Clear Type I glass vials with butyl rubber stopper containing 500 mg of rituximab in 50 mL.
Pack of 1 vial.

6.6 Special precautions for disposal and other handling

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

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

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

Medicine: keep out of reach of children

MYMabtheraIV20251124CDS35.3

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Made for

F.Hoffmann-La Roche Ltd, Basel, Switzerland

By

Roche Diagnostics GmbH, Mannheim Germany

and

By Genentech Inc., Hillsboro, Oregon, USA