

MabThera[®] 10mg/ml I.V.



Rituximab

Concentrate for solution for intravenous infusion

1. NAME OF THE MEDICINAL PRODUCT

MabThera 10mg/ml I.V.

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 indications

MabThera is indicated for the following indications:

Non-Hodgkin's lymphoma (NHL)

MabThera is indicated for the treatment of patients with relapsed or refractory low-grade or follicular, B-cell non-hodgkin's lymphoma.

MabThera is indicated for the treatment of previously untreated patients with low-grade or follicular lymphoma in combination with chemotherapy

MabThera is indicated for the treatment of patients with CD20 positive diffuse large B-cell non-Hodgkin's lymphoma in combination with CHOP chemotherapy.

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

Chronic lymphocytic leukaemia (CLL)

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

See section 5.1 for further information.

Rheumatoid arthritis

MabThera is indicated, in combination with methotrexate, to reduce signs and symptoms in adult patients with moderately to severely active rheumatoid arthritis who had an inadequate response or intolerance to one or more TNF antagonist therapies.

Granulomatosis with polyangiitis and microscopic polyangiitis

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

Pemphigus vulgaris

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

4.2 Posology and method of administration

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

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

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

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

In 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 MabThera treatment.

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

Posology

It is important to check the medicinal product labels to ensure that the appropriate formulation (intravenous or subcutaneous formulation) is being given to the patient, as prescribed.

Non-Hodgkin's lymphoma

Follicular non-Hodgkin's lymphoma

Combination therapy

The recommended dose of MabThera in combination with chemotherapy for induction treatment of previously untreated or relapsed/ refractory patients with follicular lymphoma is: 375 mg/m² body surface area per cycle, for up to 8 cycles.

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

Maintenance therapy

- Previously untreated follicular lymphoma

The recommended dose of MabThera used as a maintenance treatment for patients with previously untreated follicular lymphoma who have responded to induction treatment is: 375 mg/m² body surface area once every 2 months (starting 2 months after the last dose of induction therapy) until disease progression or for a maximum period of two years.

- Relapsed/refractory follicular lymphoma

The recommended dose of MabThera used as a maintenance treatment for patients with relapsed/refractory follicular lymphoma who have responded to induction treatment is: 375 mg/m² body surface area once every 3 months (starting 3 months after the last dose of induction therapy) until disease progression or for a maximum period of two years.

Monotherapy

- Relapsed/refractory follicular lymphoma

The recommended dose of MabThera monotherapy used as induction treatment for adult patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy is: 375 mg/m² body surface area, administered as an intravenous infusion once weekly for four weeks.

For retreatment with MabThera monotherapy for patients who have responded to previous treatment with MabThera monotherapy for relapsed/refractory follicular lymphoma, the recommended dose is: 375 mg/m² body surface area, administered as an intravenous infusion once weekly for four weeks (see section 5.1).

Diffuse large B cell non-Hodgkin's lymphoma

MabThera should be used in combination with CHOP chemotherapy. The recommended dosage is 375 mg/m² body surface area, administered on day 1 of each chemotherapy cycle for 8 cycles after intravenous infusion of the glucocorticoid component of CHOP. Safety and efficacy of MabThera

have not been established in combination with other chemotherapies in diffuse large B cell non-Hodgkin's lymphoma.

Dose adjustments during treatment

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

Chronic lymphocytic leukaemia

The recommended dosage of MabThera in combination with chemotherapy for previously untreated and relapsed/refractory patients is 375 mg/m² body surface area administered on day 0 of the first treatment cycle followed by 500 mg/m² body surface area administered on day 1 of each subsequent cycle for 6 cycles in total. The chemotherapy should be given after MabThera infusion.

Rheumatoid arthritis

A course of MabThera consists of two 1000 mg intravenous infusions. The recommended dosage of MabThera is 1000 mg by intravenous infusion followed by a second 1000 mg intravenous infusion two weeks later.

Subsequent courses should be administered every 24 weeks or based on clinical evaluation, but not sooner than every 16 weeks.

Available data suggest that clinical response is usually achieved within 16 - 24 weeks of an initial treatment course. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within this time period.

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

The recommended dosage of MabThera for induction of remission therapy of GPA and MPA is 375 mg/m² body surface area, administered as an intravenous infusion once weekly for 4 weeks (four infusions in total).

Pemphigus vulgaris

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

Maintenance treatment

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

Treatment of relapse

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

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

Special populations

Paediatric population

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

Elderly

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

Method of administration

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

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

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

First infusion

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

Subsequent infusions

All indications

Subsequent doses of MabThera can be infused at an initial rate of 100 mg/h, and increased by 100 mg/h increments at 30 minute intervals, to a maximum of 400 mg/h.

Rheumatoid arthritis only

Alternative subsequent, faster, infusion schedule

If patients did not experience a serious infusion related reaction with their first or subsequent infusions of a dose of 1000 mg MabThera administered over the standard infusion schedule, a more rapid infusion can be administered for second and subsequent infusions using the same concentration as in previous infusions (4 mg/mL in a 250 mL volume). Initiate at a rate of 250mg/hour for the first 30 minutes and then 600 mg/hour for the next 90 minutes. If the more rapid infusion is tolerated, this infusion schedule can be used when administering subsequent infusions.

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

4.3 Contraindications

Contraindications for use in non-Hodgkin's lymphoma and chronic lymphocytic leukaemia

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

Active, severe infections (see section 4.4).

Patients in a severely immunocompromised state.

Contraindications for use in rheumatoid arthritis, granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and pemphigus vulgaris

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

Active, severe infections (see section 4.4).

Patients in a severely immunocompromised state.

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

4.4 Special warnings and precautions for use

Traceability

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

Progressive multifocal leukoencephalopathy (PML)

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.

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.

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.

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.

Infections

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).

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 (see section 4.8).

Cases of hepatitis B reactivation have been reported in subjects receiving MabThera including fulminant hepatitis with fatal outcome. The majority of these subjects were also exposed to cytotoxic chemotherapy. Limited information from one study in relapsed/refractory CLL patients suggests that 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.

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

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

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

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.

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

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

Cardiac disorders

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

Infections

Based on the mechanism of action of 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.

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

Hepatitis B Infections

Cases of hepatitis B reactivation, including those with a fatal outcome, have been reported in rheumatoid arthritis, GPA and MPA patients receiving MabThera.

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.

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).

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.

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 10ml vial) and 13.2% (for 50ml 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 milk levels (relative infant dose less than 0.4%). Few cases of follow-up of breastfed infants describe normal growth and development up to 1.5 years. However, as these data are limited and the long-term outcomes of breastfed infants remain unknown, breastfeeding is not recommended while being treated with rituximab and optimally for 12 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 ADRs reported include hepatitis B reactivation and PML (see section 4.4.).

Tabulated list of adverse reactions

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

Table 1 ADRs reported in clinical trials or during postmarketing surveillance in patients with NHL and CLL disease treated with 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	
Blood and lymphatic system disorders	neutropenia, leucopenia, +febrile neutropenia, +thrombocytopenia	anaemia, +pancytopenia, +granulocytopenia	coagulation disorders, aplastic anaemia, haemolytic anaemia, lymphadenopathy		transient increase in serum IgM levels ³	late neutropenia ³
Immune system disorders	infusion related reactions ⁴ , angioedema	hypersensitivity		anaphylaxis	tumour lysis syndrome, cytokine release syndrome ⁴ , serum sickness	infusion-related acute reversible thrombocytopenia ⁴
Metabolism and nutrition disorders		hyperglycaemia, weight decrease, peripheral oedema, face oedema, increased LDH, hypocalcaemia				
Psychiatric disorders			depression, nervousness,			
Nervous system disorders		paraesthesia, hypoaesthesia, agitation, insomnia, vasodilatation, dizziness, anxiety	Dysgeusia		peripheral neuropathy, facial nerve palsy ⁵	cranial neuropathy, loss of other senses ⁵
Eye disorders		lacrimation disorder, conjunctivitis			severe vision loss ⁵	
Ear and labyrinth disorders		tinnitus, ear pain				hearing loss ⁵

MedDRA System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not known
Cardiac disorders		+myocardial infarction ^{4 and 6} , arrhythmia, +atrial fibrillation, tachycardia, +cardiac disorder	+left ventricular failure, +supraventricular tachycardia, +ventricular tachycardia, +angina, +myocardial ischaemia, bradycardia	severe cardiac disorders ^{4 and 6}	heart failure ^{4 and 6}	
Vascular disorders		hypertension, orthostatic hypotension, hypotension			vasculitis (predominately cutaneous), leukocytoclastic vasculitis	
Respiratory, thoracic and mediastinal disorders		Bronchospasm ⁴ , respiratory disease, chest pain, dyspnoea, increased cough, rhinitis	asthma, bronchiolitis obliterans, lung disorder, hypoxia	interstitial lung disease ⁷	respiratory failure ⁴ ,	lung infiltration,
Gastrointestinal disorders	nausea	vomiting, diarrhoea, abdominal pain, dysphagia, stomatitis, constipation, dyspepsia, anorexia, throat irritation	abdominal enlargement		gastro-intestinal perforation ⁷	
Skin and subcutaneous tissue disorders	pruritus, rash, +alopecia	urticaria, sweating, night sweats, +skin disorder			severe bullous skin reactions, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome) ⁷	
Musculoskeletal, connective tissue disorders		hypertonia, myalgia, arthralgia, back pain, neck pain, pain				
Renal and urinary disorders					renal failure ⁴	

MedDRA System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not known
General disorders and administration site conditions	fever, chills, asthenia, headache	tumour pain, flushing, malaise, cold syndrome, ⁺ fatigue, ⁺ shivering, ⁺ multi-organ failure ⁴	infusion site pain			
Investigations	decreased IgG levels					
<p>For each term, the frequency count was based on reactions of all grades (from mild to severe), except for terms marked with "+" where the frequency count was based only on severe (≥ grade 3 NCI common toxicity criteria) reactions. Only the highest frequency observed in the trials is reported</p> <p>¹ includes reactivation and primary infections; frequency based on R-FC regimen in relapsed/refractory CLL</p> <p>² see also section infection below</p> <p>³ see also section haematologic adverse reactions below</p> <p>⁴ see also section infusion-related reactions below. Rarely fatal cases reported</p> <p>⁵ signs and symptoms of cranial neuropathy. Occurred at various times up to several months after completion of MabThera therapy</p> <p>⁶ observed mainly in patients with prior cardiac condition and/or cardiotoxic chemotherapy and were mostly associated with infusion-related reactions</p> <p>⁷ includes fatal cases</p>						

The following terms have been reported as adverse events during clinical trials, however, were reported at a similar or lower incidence in the 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)) and hepatitis C virus. Cases of fatal PML that occurred after disease

progression and retreatment have also been reported in clinical trials. Cases of hepatitis B reactivation, have been reported, the majority of which were in patients receiving 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 Waldenstrom's macroglobulinaemia, transient increases in serum IgM levels have been observed following treatment initiation, which may be associated with hyperviscosity and related symptoms. The transient IgM increase usually returned to at least baseline level within 4 months.

Cardiovascular adverse reactions

Cardiovascular reactions during clinical trials with 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):

The incidence of ADRs of all grades and grade 3 /4 ADR was similar in elderly patients compared to younger patients (<65 years).

Bulky disease

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

Re-treatment

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

Patient subpopulations - MabThera combination therapy

Elderly (≥ 65 years)

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

Experience from rheumatoid arthritis

Summary of the safety profile

The overall safety profile of 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 $< 1/100$), and very rare ($< 1/10,000$). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The most frequent adverse reactions considered due to receipt of 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 postmarketing surveillance occurring in patients with rheumatoid arthritis receiving MabThera

MedDRA System Organ Class	Very Common	Common	Uncommon	Rare	Very rare
Infections and Infestations	upper respiratory tract infection, urinary tract infections	Bronchitis, sinusitis, gastroenteritis, tinea pedis			PML, reactivation of hepatitis B
Blood and lymphatic system disorders		neutropenia ¹		late neutropenia ²	Serum sickness-like reaction
Immune System Disorders	³ Infusion related reactions (hypertension, nausea, rash, pyrexia, pruritus, urticaria, throat irritation, hot flush, hypotension, rhinitis, rigors, tachycardia, fatigue, oropharyngeal pain, peripheral oedema, erythema)		³ Infusion related reactions (generalized oedema, bronchospasm, wheezing, laryngeal oedema, angioneurotic oedema, generalized pruritus, anaphylaxis, anaphylactoid reaction)		
General disorders and administration site conditions					
Metabolism and nutrition Disorders		hypercholesterolemia			
Psychiatric disorders		depression, anxiety			
Nervous System disorders	headache	paraesthesia, migraine, dizziness, sciatica			
Cardiac disorders				angina pectoris, atrial fibrillation, heart failure, myocardial infarction	atrial flutter
Gastrointestinal Disorders		Dyspepsia, diarrhoea, gastro-oesophageal reflux, mouth ulceration, upper abdominal pain			
Skin and Subcutaneous Tissue Disorders		alopecia			Toxic Epidermal Necrolysis (Lyell's syndrome), Stevens-Johnson syndrome ⁵
Musculo skeletal disorders and connective tissue disorders		arthralgia / musculoskeletal pain, osteoarthritis, bursitis			
Investigations	decreased IgM levels ⁴	decreased IgG levels ⁴			

¹ Frequency category derived from laboratory values collected as part of routine laboratory monitoring in clinical trials
² Frequency category derived from post-marketing data.
³ Reactions occurring during or within 24 hours of infusion. See also infusion-related reactions below. IRRs may occur as a result of hypersensitivity and/or to the mechanism of action.
⁴ Includes observations collected as part of routine laboratory monitoring.
⁵ Includes fatal cases

Multiple courses

Multiple courses of treatment are associated with a similar ADR profile to that observed following first exposure. The rate of all ADRs 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 ADRs following receipt of MabThera in clinical studies were IRRs (refer to Table 2). 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 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.

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)

In the GPA/MPA study, 99 patients were treated 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, and at a higher frequency than the comparator group.

MedDRA System organ class Adverse reaction	Rituximab (n=99)
Infections and infestations	
Urinary tract infection	7%
Bronchitis	5%
Herpes zoster	5%
Nasopharyngitis	5%
Blood and lymphatic system disorder	
Thrombocytopenia	7%
Immune system disorders	
Cytokine release syndrome	5%
Metabolism and nutrition disorders	
Hyperkalaemia	5%
Psychiatric disorders	
Insomnia	14%
Nervous system disorders	
Dizziness	10%

MedDRA System organ class Adverse reaction	Rituximab (n=99)
Tremor	10%
Vascular disorders	
Hypertension	12%
Flushing	5%
Respiratory, thoracic and mediastinal disorders	
Cough	12%
Dyspnoea	11%
Epistaxis	11%
Nasal congestion	6%
Gastrointestinal disorders	
Diarrhoea	18%
Dyspepsia	6%
Constipation	5%
Skin and subcutaneous tissue disorders	
Acne	7%
Musculoskeletal and connective tissue disorders	
Muscle spasms	18%
Arthralgia	15%
Back pain	10%
Muscle weakness	5%
Musculoskeletal pain	5%
Pain in extremities	5%
General disorders and administration site conditions	
Peripheral oedema	16%
Investigations	
Decreased haemoglobin	6%

Description of selected adverse reactions

Infusion related reactions

IRRs in the GPA and MPA clinical trial were defined as any adverse event occurring within 24 hours of an infusion and considered to be infusion-related by investigators in the safety population. Of the 99 patients treated with MabThera and 12% experienced at least one IRR. All IRRs were CTC Grade 1 or 2. The most common IRRs included cytokine release syndrome, flushing, throat irritation, and tremor. MabThera was given in combination with intravenous glucocorticoids which may reduce the incidence and severity of these events.

Infections

In the 99 MabThera patients, the overall rate of infection was approximately 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%.

Malignancies

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

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 GPA and MPA patients receiving MabThera in the postmarketing setting.

Hypogammaglobulinaemia

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

In GPA/MPA Study, 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, 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. The effect of multiple MabThera courses on the development of neutropenia in GPA and MPA patients has not been studied in clinical trials.

Skin and subcutaneous tissue disorders

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

Experience from pemphigus vulgaris

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

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

In PV Study 2, a randomized, double-blind, double-dummy, active-comparator, multicenter study evaluating the efficacy and safety of MabThera compared with mycophenolate mofetil (MMF) in patients with moderate-to-severe PV requiring oral corticosteroids, 67 PV patients received treatment with MabThera (initial 1000 mg IV on Study Day 1 and a second 1000 mg IV on Study Day 15 repeated at Weeks 24 and 26) for up to 52 weeks (see section 5.1).

The safety profile of MabThera in PV was consistent with the established safety profile in other approved autoimmune indications.

Tabulated list of adverse reactions for PV Studies 1 and 2

Adverse reactions from PV Studies 1 and 2 are presented in Table 4. In PV Study 1, ADRs were defined as adverse events which occurred at a rate of $\geq 5\%$ among MabThera-treated PV patients, with a $\geq 2\%$ absolute difference in incidence between the MabThera-treated group and the standard-dose prednisone group up to month 24. No patients were withdrawn due to ADRs in Study 1. In PV Study 2, ADRs were defined as adverse events occurring in $\geq 5\%$ of patients in the MabThera arm and assessed as related.

Table 4 Adverse reactions in MabThera-treated pemphigus vulgaris patients in PV Study 1 (up to month 24) and PV Study 2 (up to Week 52)

MedDRA System Organ Class	Very Common	Common
Infections and infestations	Upper respiratory tract infection	Herpes virus infection Herpes zoster Oral herpes Conjunctivitis Nasopharyngitis Oral candidiasis Urinary tract infection
Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)		Skin papilloma
Psychiatric disorders	Persistent depressive disorder	Major depression Irritability
Nervous system disorders	Headache	Dizziness
Cardiac disorders		Tachycardia
Gastrointestinal disorders		Abdominal pain upper
Skin and subcutaneous tissue disorders	Alopecia	Pruritus Urticaria Skin disorder
Musculoskeletal, connective tissue and bone disorders		Musculoskeletal pain Arthralgia Back pain
General disorders and administration site conditions		Fatigue Asthenia Pyrexia
Injury, Poisoning and Procedural Complications	Infusion-related reactions*	
<p>*Infusion-related reactions for PV Study 1 included symptoms collected on the next scheduled visit after each infusion, and adverse events occurring on the day of or one day after the infusion. The most common infusion-related reaction symptoms/Preferred Terms for PV Study 1 included headaches, chills, high blood pressure, nausea, asthenia and pain.</p> <p>The most common infusion-related reaction symptoms/Preferred Terms for PV Study 2 were dyspnoea, erythema, hyperhidrosis, flushing/hot flush, hypotension/low blood pressure and rash/rash pruritic.</p>		

Description of selected adverse reactions

Infusion-related reactions

In PV Study 1, Infusion-related reactions were common (58%). Nearly all infusion-related reactions were mild to moderate. The proportion of patients experiencing an infusion-related reaction was 29% (11 patients), 40% (15 patients), 13% (5 patients), and 10% (4 patients) following the first, second,

third, and fourth infusions, respectively. No patients were withdrawn from treatment due to infusion-related reactions. Symptoms of infusion-related reactions were similar in type and severity to those seen in RA and GPA/MPA patients.

In PV Study 2, IRRs occurred primarily at the first infusion and the frequency of IRRs decreased with subsequent infusions: 17.9%, 4.5%, 3% and 3% of patients experienced IRRs at the first, second, third, and fourth infusions, respectively. In 11/15 patients who experienced at least one IRR, the IRRs were Grade 1 or 2. In 4/15 patients, Grade ≥ 3 IRRs were reported and led to discontinuation of MabThera treatment; three of the four patients experienced serious (life-threatening) IRRs. Serious IRRs occurred at the first (2 patients) or second (1 patient) infusion and resolved with symptomatic treatment.

Infections

In PV Study 1, 14 patients (37%) in the MabThera group experienced treatment-related infections compared to 15 patients (42%) in the standard-dose prednisone group. The most common infections in the MabThera group were herpes simplex and zoster infections, bronchitis, urinary tract infection, fungal infection and conjunctivitis. Three patients (8%) in the MabThera group experienced a total of 5 serious infections (*Pneumocystis jirovecii* pneumonia, infective thrombosis, intervertebral discitis, lung infection, *Staphylococcal* sepsis) and one patient (3%) in the standard-dose prednisone group experienced a serious infection (*Pneumocystis jirovecii* pneumonia).

In PV Study 2, 42 patients (62.7%) in the MabThera arm experienced infections. The most common infections in the MabThera group were upper respiratory tract infection, nasopharyngitis, oral candidiasis and urinary tract infection. Six patients (9%) in the MabThera arm experienced serious infections.

Laboratory abnormalities

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

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form <https://sideeffects.health.gov.il>

4.9 Overdose

Limited experience with doses higher than the approved dose of intravenous MabThera formulation 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 CLL. No additional safety signals were identified.

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

In the postmarketing 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, ATC code: L01X C02

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 CD 20 antigen on B lymphocytes has also been demonstrated to induce cell death via apoptosis.

Peripheral B cell counts declined below normal following completion of the first dose of 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 experience in Non-Hodgkin's lymphoma and in chronic lymphocytic leukaemia

Follicular lymphoma

Monotherapy

Initial treatment, weekly for 4 doses

In the pivotal trial, 166 patients with relapsed or chemoresistant low-grade or follicular B cell NHL received 375 mg/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 % (CI₉₅ % 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 ≥ 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 % (CI₉₅ % 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 % (CI₉₅ % 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 5.

Table 5 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 6).

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 6). 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 6).

Table 6 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 7).

Table 7 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 8 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 8). 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.

Adult Diffuse large B cell non-Hodgkin's lymphoma

In a randomised, open-label trial, a total of 399 previously untreated elderly patients (age 60 to 80 years) with diffuse large B cell lymphoma received standard CHOP chemotherapy (cyclophosphamide 750 mg/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 9a and Table 9b) and 552 patients (276 R-FC, 276 FC) for the relapsed/refractory study (Table 10) 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 9a). 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 9b).

Table 9a 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%

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 9b 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 10 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.

Paediatric population

See Section 4.2 for information on paediatric use.

Clinical experience 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, multicenter trial (Trial 1).

Trial 1 evaluated 517 patients that had experienced an inadequate response or intolerance to one or more TNF inhibitor therapies. Eligible patients had active rheumatoid arthritis, diagnosed according to the criteria of the American College of Rheumatology (ACR). 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 11). 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 11 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 11).

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 12).

Table 12 Radiographic outcomes at 1 year (mITT population)

	Placebo+MTX	MabThera+MTX 2 × 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 13).

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 13).

Table 13 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: * $p < 0.05$, ** $p < 0.001$ *** $p \leq 0.0001$
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.

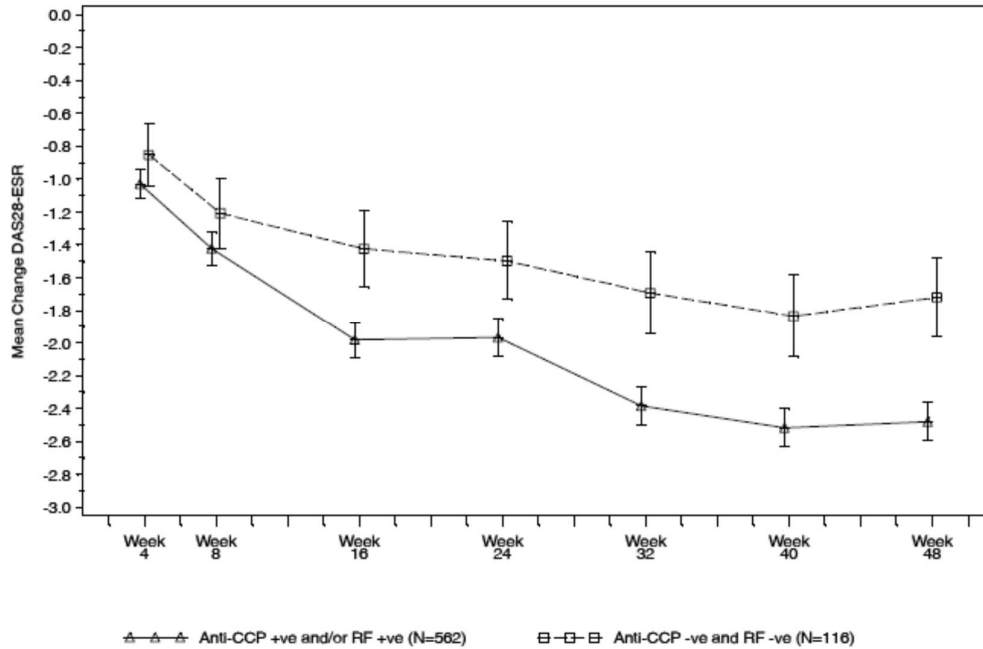
Efficacy outcomes in MabThera treated patients were analysed based on autoantibody status prior to commencing treatment. At Week 24, patients who were seropositive to RF and/or anti-CCP at baseline had a significantly increased probability of achieving ACR20 and 50 responses compared to seronegative patients ($p=0.0312$ and $p=0.0096$) (Table 14). 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 14 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 * $p < 0.05$, ** $p < 0.001$, *** $p < 0.0001$.

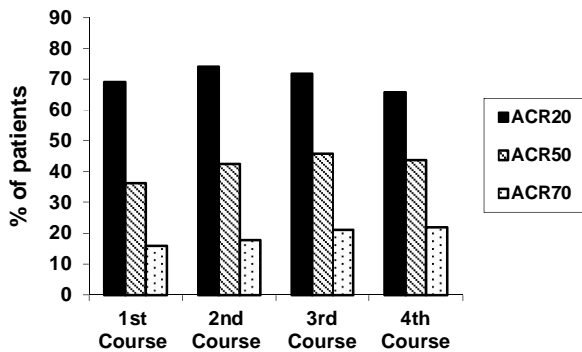
Figure 1: Change from baseline of DAS28-ESR by baseline autoantibody status



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.

Paediatric population

See Section 4.2 for information on paediatric use.

Clinical Experience in granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA)

Adult induction of remission

In GPA/MPA Study, 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, multicenter, non-inferiority trial.

Patients were randomised in a 1:1 ratio to receive either oral cyclophosphamide daily (2 mg/kg/day) for 3-6 months or 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 15).

Efficacy was observed both for patients with newly diagnosed disease and for patients with relapsing disease (Table 16).

Table 15 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 16 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.

Retreatment with MabThera

Based upon investigator judgment, 15 patients received a second course of MabThera therapy for treatment of relapse of disease activity which occurred between 6 and 18 months after the first course of MabThera. The limited data from the present trial preclude any conclusions regarding the efficacy of subsequent courses of MabThera in patients with GPA and MPA.

Continued immunosuppressive therapy may be especially appropriate in patients at risk for relapses (i.e. with history of earlier relapses and GPA, or patients with reconstitution of B-lymphocytes in addition to PR3-ANCA at monitoring). When remission with MabThera has been achieved, continued immunosuppressive therapy may be considered to prevent relapse. The efficacy and safety of MabThera in maintenance therapy has not been established.

Laboratory Evaluations

A total of 23/99 (23%) MabThera-treated patients from the 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.

Clinical experience in pemphigus vulgaris

PV Study 1 (Study ML22196)

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

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

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

PV Study 1 Results

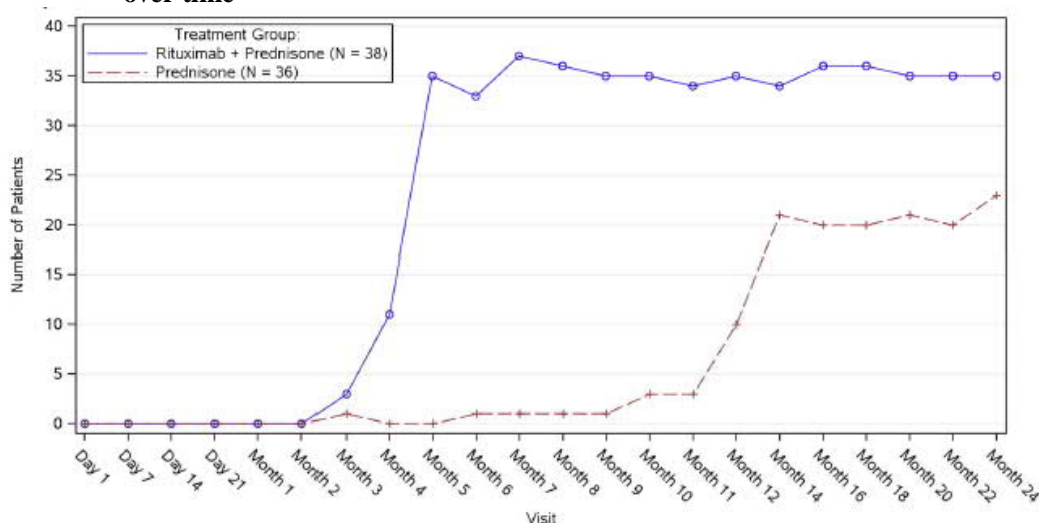
The study showed statistically significant results of MabThera and low-dose prednisone over standard-dose prednisone in achieving CROff ≥ 2 months at month 24 in PV patients (see Table 17).

Table 17 Percentage of PV patients who achieved complete remission off corticosteroid therapy for two months or more at month 24 (Intent-to-Treat Population - PV)

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

The number of rituximab plus low-dose prednisone patients off prednisone therapy or on minimal therapy (prednisone dose of 10 mg or less per day) compared to standard-dose prednisone patients over the 24-month treatment period shows a steroid-sparing effect of MabThera (Figure 3).

Figure 3: Number of patients who were off or on minimal corticosteroid (≤ 10 mg/day) therapy over time



Post-hoc retrospective laboratory evaluation

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

PV Study 2 (Study WA29330)

In a randomized, double-blind, double-dummy, active-comparator, multicenter study, the efficacy and safety of MabThera compared with mycophenolate mofetil (MMF) were evaluated in patients with moderate-to-severe PV receiving 60-120 mg/day oral prednisone or equivalent (1.0-1.5 mg/kg/day) at study entry and tapered to reach a dose of 60 or 80 mg/day by Day 1. Patients had a confirmed diagnosis of PV within the previous 24 months and evidence of moderate-to-severe disease (defined as a total Pemphigus Disease Area Index, PDAI, activity score of ≥ 15).

One hundred and thirty-five patients were randomized to treatment with MabThera 1000 mg administered on Day 1, Day 15, Week 24 and Week 26 or oral MMF 2 g/day for 52 weeks in combination with 60 or 80 mg oral prednisone with the aim of tapering to 0 mg/day prednisone by Week 24.

The primary efficacy objective for this study was to evaluate at week 52, the efficacy of MabThera compared with MMF in achieving sustained complete remission defined as achieving healing of lesions with no new active lesions (i.e., PDAI activity score of 0) while on 0 mg/day prednisone or equivalent, and maintaining this response for at least 16 consecutive weeks, during the 52-week treatment period.

PV Study 2 Results

The study demonstrated the superiority of MabThera over MMF in combination with a tapering course of oral corticosteroids in achieving CRoff corticosteroid \geq 16 weeks at Week 52 in PV patients (Table 18). The majority of patients in the mITT population were newly diagnosed (74%) and 26% of patients had established disease (duration of illness \geq 6 months and received prior treatment for PV).

Table 18 Percentage of PV Patients Who Achieved Sustained Complete Remission Off Corticosteroid Therapy for 16 Weeks or More at Week 52 (Modified Intent-to-Treat Population)

	MabThera (N=62)	MMF (N=63)	Difference (95% CI)	p-value
Number of responders (response rate [%])	25 (40.3%)	6 (9.5%)	30.80% (14.70%, 45.15%)	<0.0001
Newly diagnosed patients	19 (39.6%)	4 (9.1%)		
Patients with established disease	6 (42.9%)	2 (10.5%)		
MMF = Mycophenolate mofetil. CI = Confidence Interval. Newly diagnosed patients = duration of illness < 6 months or no prior treatment for PV. Patients with established disease = duration of illness \geq 6 months and received prior treatment for PV. Cochran-Mantel-Haenszel test is used for p-value.				

The analysis of all secondary parameters (including cumulative oral corticosteroid dose, the total number of disease flares, and change in health-related quality of life, as measured by the Dermatology Life Quality Index) verified the statistically significant results of MabThera compared to MMF. Testing of secondary endpoints were controlled for multiplicity.

Glucocorticoid exposure

The cumulative oral corticosteroid dose was significantly lower in patients treated with MabThera. The median (min, max) cumulative prednisone dose at Week 52 was 2775 mg (450, 22180) in the MabThera group compared to 4005 mg (900, 19920) in the MMF group (p=0.0005).

Disease flare

The total number of disease flares was significantly lower in patients treated with MabThera compared to MMF (6 vs. 44, p<0.0001) and there were fewer patients who had at least one disease flare (8.1% vs. 41.3%).

Laboratory evaluations

By week 52, a total of 20/63 (31.7%) (19 treatment-induced and 1 treatment-enhanced) MabThera - treated PV patients tested positive for ADA. There was no apparent negative impact of the presence of ADA on safety or efficacy in PV Study 2.

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 2 x 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 × 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.

Pemphigus vulgaris

The PK parameters in adult PV patients receiving MabThera 1000 mg at Days 1, 15, 168, and 182 are summarized in Table 19.

Table 19 Population PK in adult PV patients from PV Study 2

Parameter	Infusion Cycle	
	1st cycle of 1000 mg Day 1 and Day 15 N=67	2nd cycle of 1000 mg Day 168 and Day 182 N=67
Terminal Half-life (days)		
Median	21.0	26.5
(Range)	(9.3-36.2)	(16.4-42.8)
Clearance (L/day)		
Mean	391	247
(Range)	(159-1510)	(128-454)
Central Volume of Distribution (L)		
Mean	3.52	3.52
(Range)	(2.48-5.22)	(2.48-5.22)

Following the first two rituximab administrations (at day 1 and 15, corresponding to cycle 1), the PK parameters of rituximab in patients with PV were similar to those in patients with GPA/MPA and patients with RA. Following the last two administrations (at day 168 and 182, corresponding to cycle 2), rituximab clearance decreased while the central volume of distribution remained unchanged.

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 post nately 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

Citrate ions
Sodium chloride
Polysorbate 80
Sodium hydroxide
Hydrochloric acid
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:

The expiry date of the product is indicated on the packaging materials.

Diluted medicinal product:

- After aseptic dilution in sodium chloride solution

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

- After aseptic dilution in D-glucose solution

The prepared infusion solution of MabThera in 5% D-glucose solution is physically and chemically stable for 24 hours at 2 °C - 8 °C and plus 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 in a refrigerator (2°C – 8°C). Keep the container in the outer carton in order to protect from light.

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

6.5 Nature and contents of container

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% D-Glucose in water. For mixing the solution, gently invert the bag in order to avoid foaming. Care must be taken to ensure the sterility of prepared solutions. Since the medicinal product does not contain any anti-microbial preservative or bacteriostatic agents, aseptic technique must be observed. Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration.

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

7. MARKETING AUTHORISATION HOLDER

Roche Pharmaceuticals (Israel) Ltd., P.O. Box 6391, Hod Hasharon 4524079.

8. MARKETING AUTHORISATION NUMBER(S)

MABTHERA 10mg/ml I.V.

112.51.29472.00

9. MANUFACTURER

F. Hoffmann-La Roche Ltd., Basel, Switzerland.

<i>Medicine: keep out of reach of children</i>
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Revised on October 2021 according to MOHs guidelines