**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

MabThera 100 mg concentrate for solution for infusion

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 10 mg of rituximab.

Each single-use vial containing 100 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.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear, colourless liquid.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

MabThera is indicated in adults for the following indications:

Non-Hodgkin's lymphoma (NHL)

MabThera is indicated for the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy.

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

MabThera monotherapy is indicated for treatment of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy.

MabThera is indicated for the treatment of patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy.

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

MabThera has been shown to reduce the rate of progression of joint damage as measured by x-ray and to improve physical function, when given in combination with methotrexate.

Granulomatosis with polyangiitis and Microscopic polyangiitis

MabThera, in combination with glucocorticoids, is indicated for the induction of remission in adult patients with severe, active Granulomatosis with polyangiitis (Wegener's) (GPA) and Microscopic polyangiitis (MPA).

## 4.2 Posology and method of administration

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

Posology

*Non-Hodgkin's lymphoma*

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

*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/m$^2$ 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/m$^2$ body surface area once every 2 months (starting 2 months after the last dose of induction therapy) until disease progression or for a maximum period of two years.

*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/m$^2$ body surface area once every 3 months (starting 3 months after the last dose of induction therapy) until disease progression or for a maximum period of two years.

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/m$^2$ 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/m$^2$ 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/m$^2$ body surface area, administered on day 1 of each chemotherapy cycle for 8 cycles after intravenous infusion of the glucocorticoid component of CHOP. Safety and efficacy of MabThera have not been established in combination with other chemotherapies in diffuse large B cell non-Hodgkin's lymphoma.

*Chronic lymphocytic leukaemia*

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

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

*Rheumatoid arthritis*

Patients treated with MabThera must be given the patient alert card with each infusion (see Annex IIIA – Labelling).

Patients should receive treatment with 100 mg intravenous methylprednisolone to be completed 30 minutes prior to MabThera infusions to decrease the incidence and severity of infusion related reactions. Premedication consisting of an analgesic/anti-pyretic (*e.g. paracetamol*) and an anti-histaminic drug (*e.g. diphenhydramine*) should always be administered before each infusion of MabThera (see section 4.4).

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.

The need for further courses should be evaluated 24 weeks following the previous course. Retreatment should be given at that time if residual disease activity remains, otherwise retreatment should be delayed until disease activity returns.

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

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

*Second infusion of each course*
Subsequent doses of MabThera can be infused at an initial rate of 100 mg/hr, and increased by 100 mg/hr increments at 30 minute intervals, to a maximum of 400 mg/hr.

*Granulomatosis with polyangiitis and Microscopic polyangiitis*

Patients treated with MabThera must be given the patient alert card with each infusion (see Annex IIIA – Labelling).

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

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

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 80mg/day, and tapered as rapidly as possible based on clinical need) during and after MabThera treatment.

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

Subsequent infusions (number 2 to 4): Subsequent infusions of MabThera can be started at a rate of 100 mg/h and increased by 100 mg/h increments every 30 minutes to a maximum of 400 mg/h.

Pneumocystis jiroveci pneumonia (PCP) prophylaxis is recommended for patients with Granulomatosis with polyangiitis or Microscopic polyangiitis during and following MabThera treatment, as appropriate.

*Special populations*

*Paediatric population*
The safety and efficacy of MabThera in children has not been established.

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

Method of administration

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

In Rheumatoid Arthritis, premedication with glucocorticoids should also be administered in order to reduce the frequency and severity of infusion-related reactions.

Premedication with glucocorticoids should be considered if MabThera is not given in combination with glucocorticoid-containing chemotherapy for treatment of non-Hodgkin's lymphoma and chronic lymphocytic leukaemia.

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

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

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 (section 4.8) usually respond to a reduction in the rate of infusion. The infusion rate may be increased upon improvement of symptoms.

## 4.3 Contraindications

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

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

Active, severe infections (see section 4.4).

Patients in a severely immunocompromised state

Contraindications for use in rheumatoid arthritis, Granulomatosis with polyangiitis and Microscopic polyangiitis

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

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

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

Progressive multifocal leukoencephalopathy

All patients treated with MabThera for rheumatoid arthritis, Granulomatosis with polyangiitis and Microscopic polyangiitis must be given the patient alert card with each infusion (see end of Annex IIIA - Labelling). The alert card contains important safety information for patients regarding potential increased risk of infections, including 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, 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 reactions*

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 only 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.

***Severe cytokine release syndrome*** is characterised by severe dyspnea, 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, hyperphosphatemia, 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.

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

greactions 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 infusion, 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 x $10^9$/l and/or platelet counts < 75 x $10^9$/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.

*Immunizations*
The safety of immunization 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-randomized study, patients with relapsed low-grade NHL who received

MabThera monotherapy when compared to healthy untreated controls had a lower rate of response to vaccination with tetanus recall antigen (16% vs. 81%) and Keyhole Limpet Haemocyanin (KLH) neoantigen (4% vs. 76% when assessed for >2-fold increase in antibody 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 titers 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, treatment should be permanently discontinued.

Rheumatoid arthritis, Granulomatosis with polyangiitis and Microscopic polyangiitis

*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 (IRR), which may be related to release of cytokines and/or other chemical mediators. Premedication consisting of an analgesic/anti-pyretic drug and an anti-histaminic drug, should always be administered before each infusion of MabThera. In Rheumatoid arthritis premedication with glucocorticoids should also be administered before each infusion of MabThera in order to reduce the frequency and severity of infusion-related reactions (see section 4.2 and section 4.8).

Severe infusion-related reactions 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 infusion-related reaction 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.

Infusion-related reactions for patients with Granulomatosis with polyangiitis and Microscopic polyangiitis were similar to those seen for Rheumatoid arthritis patients in clinical trials (*see section 4.8*).

*Cardiac disorders*
Angina pectoris, cardiac 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, Granulomatosis with polyangiitis and Microscopic polyangiitis 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, treatment should be permanently discontinued.

*Immunization*
Physicians should review the patient’s vaccination status and follow current immunization guidelines prior to MabThera therapy. Vaccination should be completed at least 4 weeks prior to first administration of MabThera.

The safety of immunization 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 randomized study, patients with RA treated with MabThera and methotrexate had comparable response rates to tetanus recall antigen (39% vs. 42%), reduced rates to pneumococcal polysaccharide vaccine (43% vs. 82% to at least 2 pneumococcal antibody serotypes), and KLH neoantigen (47% vs. 93%), when given 6 months after MabThera as compared to patients only receiving methotrexate. Should non-live vaccinations be required whilst receiving MabThera therapy, these should be completed at least 4 weeks prior to commencing the next course of MabThera.

In the overall experience of MabThera repeat treatment over one year in Rheumatoid arthritis, the proportions of patients with positive antibody titers 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. On the basis of limited experience with MabThera in rheumatoid arthritis patients (see section 4.8) the present data do not seem to suggest any increased risk of malignancy. However, the possible risk for the development of solid tumours cannot be excluded at this time.

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

In patients with rheumatoid arthritis, 283 patients received subsequent therapy with a biologic DMARD following MabThera. In these patients the rate of clinically relevant infection while on MabThera was 6.01 per 100 patient years compared to 4.97 per 100 patient years following treatment with the biologic DMARD.

## 4.6 Fertility, pregnancy and lactation

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. For these reasons MabThera should not be administered to pregnant women unless the possible benefit outweighs the potential risk.

Developmental toxicity studies performed in cynomolgus monkeys revealed no evidence of embryotoxicity in utero. New born offspring of maternal animals exposed to MabThera were noted to have depleted B cell populations during the post natal phase.

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

Breast-feeding
Whether rituximab is excreted in human milk is not known. However, because maternal IgG is excreted in human milk, and rituximab was detectable in milk from lactating monkeys, women should not breastfeed while treated with MabThera and for 12 months following MabThera treatment.

Fertility
There are no data currently available on the effects of MabThera on fertility.

## 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 events reported to date do not indicate that such an effect is likely.

## 4.8 Undesirable effects

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

The overall safety profile of MabThera in non-Hodgkin's lymphoma and chronic lymphocytic leukaemia is based on data from patients from clinical trials and from post-marketing surveillance. These patients were treated either with MabThera monotherapy (as induction treatment or maintenance treatment following induction treatment) or in combination with chemotherapy.

The most frequently observed adverse drug reactions (ADRs) in patients receiving MabThera were infusion-related reactions which occurred in the majority of patients during the first infusion. The incidence of infusion-related symptoms decreases substantially with subsequent infusions and is less than 1 % after eight doses of MabThera.

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

The most frequent reported or observed serious adverse drug reactions were:
- Infusion-related reactions (including cytokine-release syndrome, tumour-lysis syndrome), 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.).

The frequencies of ADRs reported with MabThera alone or in combination with chemotherapy are summarised in Table 1. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1000) and very rare (< 1/10,000). 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**

| System Organ Class | Very Common | Common | Uncommon | Rare | Very Rare | Not known[8] |
|---|---|---|---|---|---|---|
| **Infections and infestations** | bacterial infections, viral infections, [+]bronchitis | sepsis, [+]pneumonia, [+]febrile infection, [+]herpes zoster, [+]respiratory tract infection, fungal infections, infections of unknown aetiology, [+]acute bronchitis, [+]sinusitis, hepatitis B[1] | | serious viral infection[2] Pneumocystis jirovecii | PML | |
| **Blood and lymphatic system disorders** | neutropenia, leucopenia, [+]febrile neutropenia, [+]thrombocytopenia | anaemia, [+]pancytopenia, [+]granulocytopenia | coagulation disorders, aplastic anaemia, haemolytic anaemia, lymphadenopathy | | transient increase in serum IgM levels[3] | late neutropenia[3] |
| **Immune system disorders** | infusion related reactions[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] |

| System Organ Class | Very Common | Common | Uncommon | Rare | Very Rare | Not known[8] |
|---|---|---|---|---|---|---|
| **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 events [4 and 6] | heart failure[4 and 6] | |
| **Vascular disorders** | | hypertension, orthostatic hypotension, hypotension | | | vasculitis (predominately cutaneous), leukocytoclastic vasculitis | |
| **Respiratory, thoracic and mediastinal disorders** | | Bronchospasm[4], respiratory disease, chest pain, dyspnoea, increased cough, rhinitis | asthma, bronchiolitis obliterans, lung disorder, hypoxia | interstitial lung disease[7] | respiratory failure[4], | lung infiltration, |
| **Gastrointestinal disorders** | nausea | vomiting , diarrhoea, abdominal pain, dysphagia, stomatitis, constipation, dyspepsia, anorexia, throat irritation | abdominal 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 and bone disorders** | | hypertonia, myalgia, arthralgia, back pain, neck pain, pain | | | | |
| **Renal and urinary disorders** | | | | | renal failure[4] | |

| System Organ Class | Very Common | Common | Uncommon | Rare | Very Rare | Not known[8] |
|---|---|---|---|---|---|---|
| **General disorders and administration site conditions** | fever , chills, asthenia, headache | tumour pain, flushing, malaise, cold syndrome, [+]fatigue, [+]shivering, [+]multi-organ failure[4] | infusion site pain | | | |
| **Investigations** | decreased IgG levels | | | | | |

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

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

[2] see also section infection below

[3] see also section haematologic adverse reactions below

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

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

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

[7] includes fatal cases

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

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

*Infusion-related reactions*

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 events (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.

*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.

Localized candida infections as well as Herpes zoster was reported at a higher incidence in the MabThera-containing arm of randomized 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 hematopoetic 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 subjects 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 $1x10^9$/L between day 24 and 42 after the last dose) or occurred with a late onset (defined as neutrophil count below $1x10^9$/L later than 42 days after last dose in patients with no previous prolonged neutropenia or who recovered prior to day 42) following treatment with 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 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 ischemia) 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 events*
During the treatment period, 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 recognized 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 pediatric 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*
Older people (≥ 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*
Older people (≥ 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*

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 summarized 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. Events are listed in Table 2. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), and very rare (<1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The most frequent adverse reaction considered due to receipt of MabThera were infusion related reactions. 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 drug reactions reported in clinical trials or during postmarketing surveillance occurring in patients with rheumatoid arthritis receiving MabThera**

| System Organ Class | Very Common | Common | Uncommon | Rare | Very rare |
|---|---|---|---|---|---|
| **Infections and Infestations** | upper respiratory tract 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 |
| **Cardiac Disorders** | | | | Angina pectoris, atrial fibrillation, heart failure, myocardial infarction | Atrial flutter |
| **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 pruritis, anaphylaxis, anaphylactoid reaction) | | |
| **General disorders and administration site conditions** | | | | | |
| **Metabolism and Nutritional Disorders** | | hypercholesterolemia | | | |
| **Nervous System disorders** | headache | paraesthesia, migraine, dizziness, sciatica | | | |
| **Skin and Subcutaneous Tissue Disorders** | | alopecia | | | Toxic Epidermal Necrolysis (Lyell's Syndrome), Stevens-Johnson Syndrome[5] |
| **Psychiatric Disorders** | | depression, anxiety | | | |
| **Gastrointestinal Disorders** | | Dyspepsia, diarrhoea, gastro-oesophageal reflux, mouth ulceration, upper abdominal pain | | | |
| **Musculo skeletal 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. Infusion related reactions may occur as a result of hypersensitivity and/or to the mechanism of action.
[4] Includes observations collected as part of routine laboratory monitoring.
[5] Includes fatal cases

*Multiple courses*
Multiple courses of treatment are associated with a similar 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 infusion-related reactions (most frequent during the first treatment course), RA exacerbation and infections, all of which were more frequent in the first 6 months of treatment.

*Infusion-related reactions*
The most frequent ADRs following receipt of MabThera in clinical studies were infusion-related reactions (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 decline for all subsequent infusions. In clinical studies 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 section 4.2 and 4.4). Severe infusion-related reactions with fatal outcome have been reported in the post-marketing setting.

*Infections*
The overall rate of infection was approximately 94 per 100 patient years in MabThera treated patients. The infections were predominately mild to moderate and consisted mostly of upper respiratory tract infections and urinary tract infections. The incidence of infections that were serious or required IV antibiotic was approximately 4 per 100 patient years. The rate of serious infections did not show any significant increase following multiple courses of MabThera. Lower respiratory tract infections (including pneumonia) have been reported during clinical trials, at a similar incidence in the MabThera arms compared to control arms.

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*
Serious cardiac events were reported at a rate of 1.3 per 100 patient years in the MabThera treated patients compared to 1.3 per 100 patients years in placebo treated patients. The proportions of patients experiencing cardiac events (all or serious) did not increase over multiple courses.

*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 pediatric 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 and Microscopic polyangiitis*

In the clinical study in Granulomatosis with polyangiitis and Microscopic polyangitis, 99 patients were treated with MabThera (375 mg/m$^2$, 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 ≥ 5% in the MabThera group.

**Table 3. Adverse Drug Reactions occurring at 6-months in ≥ 5% of patients receiving MabThera, and at a higher frequency than the comparator group, in the pivotal clinical study.**

| **Body System**<br><br>**Adverse event** | **Rituximab**<br><br>**(n=99)** |
|---|---|
| **Blood and lymphatic system disorders** | |
| Thrombocytopenia | 7% |
| **Gastrointestinal disorders** | |
| Diarrhoea | 18% |
| Dyspepsia | 6% |
| Constipation | 5% |
| **General disorders and administration site conditions** | |
| Peripheral oedema | 16% |
| **Immune system disorders** | |
| Cytokine release syndrome | 5% |

| **Body System**<br><br>**Adverse event** | **Rituximab**<br><br>**(n=99)** |
|---|---|
| **Infections and infestations** | |
| Urinary tract infection | 7% |
| Bronchitis | 5% |
| Herpes zoster | 5% |
| Nasopharyngitis | 5% |
| **Investigations** | |
| Decreased haemoglobin | 6% |
| **Metabolism and nutrition disorders** | |
| Hyperkalaemia | 5% |
| **Musculoskeletal and connective tissue disorders** | |
| Muscle spasms | 18% |
| Arthralgia | 15% |
| Back pain | 10% |
| Muscle weakness | 5% |
| Musculoskeletal pain | 5% |
| Pain in extremities | 5% |
| **Nervous system disorders** | |
| Dizziness | 10% |
| Tremor | 10% |
| **Psychiatric disorders** | |
| Insomnia | 14% |

| Body System<br><br>Adverse event | Rituximab<br><br>(n=99) |
|---|---|
| **Respiratory, thoracic and mediastinal disorders** | |
| Cough | 12% |
| Dyspnoea | 11% |
| Epistaxis | 11% |
| Nasal congestion | 6% |
| **Skin and subcutaneous tissue disorders** | |
| Acne | 7% |
| **Vascular disorders** | |
| Hypertension | 12% |
| Flushing | 5% |

**Further information on selected adverse drug reactions:**

*Infusion-related reactions:*

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

*Infections:*

In the 99 MabThera patients, the overall rate of infection was approximately 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 Granulomatosis with polyangiitis and Microscopic polyangiitis clinical study was 2.00 per 100 patient years at the study common closing date (when the final patient had completed the follow-up period). On the basis of standardized incidence ratios, the incidence of malignancies appears to be similar to that previously reported in patients with ANCA-associated vasculitis.

*Cardiovascular*
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).

*Hepatitis-B reactivation*
A small number of cases of hepatitis-B reactivation, some with fatal outcome, have been reported in Granulomatosis with polyangiitis and Microscopic polyangiitis patients receiving MabThera in the postmarketing setting.

*Hypogammaglobulinaemia*
Hypogammaglobulinaemia (IgA, IgG or IgM below the lower limit of normal) has been observed in Granulomatosis with polyangiitis and Microscopic polyangiitis patients treated with MabThera. At 6 months, in the active-controlled, randomized, double-blind, multicenter, non-inferiority study, 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. There was no increased rate in overall infections or serious infections in patients with low IgA, IgG or IgM.

*Neutropenia*
In the active-controlled, randomized, double-blind, multicenter, non-inferiority study of MabThera in Granulomatosis with polyangiitis and Microscopic polyangiitis, 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 Granulomatosis with polyangiitis and Microscopic polyangiitis 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.

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

## 4.9 Overdose

There has been no experience of overdose in human clinical trials. However, single doses higher than 1000 mg have not been tested in controlled clinical trials in patients with autoimmune disease. The highest dose tested to date is 5g in patients with chronic lymphocytic leukaemia. No additional safety signals were identified.

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: 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 Fcγ 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 hematological 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 Granulomatosis with polyangiitis or Microscopic polyangiitis, the number of peripheral blood B cells decreased to <10 cells/µL after two weekly infusions of rituximab 375 mg/m$^2$, and remained at that level in most patients up to the 6 month timepoint. The majority of patients (81%) showed signs of B cell return, with counts >10 cells/µL by month 12, increasing to 87% of patients by month 18.

Clinical Experience in Non-Hodgkin's lymphoma and in chronic lymphocytic leukaemia

*Follicular lymphoma*

*Monotherapy*
Initial treatment, weekly for 4 doses
In the pivotal study, 166 patients with relapsed or chemoresistant low-grade or follicular B cell NHL received 375 mg/m$^2$ of MabThera as an intravenous infusion once weekly for four weeks. The overall response rate (ORR) in the intent-to-treat (ITT) population was 48 % ($CI_{95}$ % 41 % - 56 %) with a 6 % complete response (CR) and a 42 % partial response (PR) rate. The projected median time to progression (TTP) for responding patients was 13.0 months. In a subgroup analysis, the ORR was higher in patients with IWF B, C, and D histological subtypes as compared to IWF A subtype (58 % vs. 12 %), higher in patients whose largest lesion was < 5 cm vs. > 7 cm in greatest diameter (53 % vs. 38 %), and higher in patients with chemosensitive relapse as compared to chemoresistant (defined as duration of response < 3 months) relapse (50 % vs. 22 %). ORR in patients previously treated with autologous bone marrow transplant (ABMT) was 78 % versus 43 % in patients with no ABMT. Neither age, sex, lymphoma grade, initial diagnosis, presence or absence of bulky disease, normal or high LDH nor presence of extranodal disease had a statistically significant effect (Fisher's exact test) on response to MabThera. A statistically significant correlation was noted between response rates and bone marrow involvement. 40 % of patients with bone marrow involvement responded compared to

59 % of patients with no bone marrow involvement (p=0.0186). This finding was not supported by a stepwise logistic regression analysis in which the following factors were identified as prognostic factors: histological type, bcl-2 positivity at baseline, resistance to last chemotherapy and bulky disease.

Initial treatment, weekly for 8 doses
In a multi-centre, single-arm study, 37 patients with relapsed or chemoresistant, low grade or follicular B cell NHL received 375 mg/$m^2$ 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 studies, 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 % ($CI_{95}$ % 21 % – 51 %; CR 3 %, PR 33 %) with a median TTP for responding patients of 9.6 months (range 4.5 to 26.8 months).

Re-treatment, weekly for 4 doses
In a multi-centre, single-arm study, 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/$m^2$ of MabThera as intravenous infusion weekly for four doses. Three of the patients had received two courses of MabThera before enrollment and thus were given a third course in the study. Two patients were re-treated twice in the study. For the 60 re-treatments on study, the ORR was 38 % ($CI_{95}$ % 26 % – 51 %; 10 % CR, 28 % PR) with a projected median TTP for responding patients of 17.8 months (range 5.4 – 26.6). This compares favourably with the TTP achieved after the prior course of MabThera (12.4 months).

*Initial treatment, in combination with chemotherapy*
In an open-label randomised trial, a total of 322 previously untreated patients with follicular lymphoma were randomised to receive either CVP chemotherapy (cyclophosphamide 750 mg/$m^2$, vincristine 1.4 mg/$m^2$ up to a maximum of 2 mg on day 1, and prednisolone 40 mg/$m^2$/day on days 1 -5) every 3 weeks for 8 cycles or MabThera 375 mg/$m^2$ 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 center): 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 randomized 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 summarized in table 4.

**Table 4 Summary of key results from four phase III randomized 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 mo | OS rates, % |
|---|---|---|---|---|---|---|
| **M39021** | CVP, 159<br>R-CVP, 162 | 53 | 57<br>81 | 10<br>41 | Median TTP:<br>14.7<br>33.6<br>P<0.0001 | 53-months<br>71.1<br>80.9<br>p=0.029 |
| **GLSG'00** | CHOP, 205<br>R-CHOP, 223 | 18 | 90<br>96 | 17<br>20 | Median TTF: 2.6 years<br>Not reached<br>p < 0.001 | 18-months<br>90<br>95<br>p = 0.016 |
| **OSHO-39** | MCP, 96<br>R-MCP, 105 | 47 | 75<br>92 | 25<br>50 | Median PFS: 28.8<br>Not reached<br>p < 0.0001 | 48-months<br>74<br>87<br>p = 0.0096 |
| **FL2000** | CHVP-IFN, 183<br>R-CHVP-IFN, 175 | 42 | 85<br>94 | 49<br>76 | Median EFS: 36<br>Not reached<br>p < 0.0001 | 42-months<br>84<br>91<br>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-center, 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 randomized 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/m$^2$ body surface area given every 2 months until disease progression or for a maximum period of two years.

After a median observation time of 25 months from randomization, maintenance therapy with MabThera resulted in a clinically relevant and statistically significant improvement in the primary endpoint of investigator assessed progression-free survival (PFS) as compared to observation in patients with previously untreated follicular lymphoma (Table 5).

Significant benefit from maintenance treatment with MabThera was also seen for the secondary endpoints event-free survival (EFS), time to next anti-lymphoma treatment (TNLT) time to next chemotherapy (TNCT) and overall response rate (ORR) (Table 5). The results of the primary analysis were confirmed with longer follow-up (median observation time: 48 months), and have been added to Table 5 to show the comparison between the 25 and 48 month follow up periods.

**Table 5 Maintenance phase: overview of efficacy results MabThera vs. observation after 48 months median observation time (compared with results of primary analysis based on 25 months median observation time)**

| | **Observation N=513** | **MabThera N=505** | **Log-rank P value** | **Risk reduction** |
|---|---|---|---|---|
| **Primary Efficacy** | | | | |
| PFS (median) | 48.4 months (NR) | NR (NR) | <0.0001 (<0.0001) | 45% (50%) |
| **Secondary Efficacy** | | | | |
| EFS (median) | 47.6 months (37.8 months) | NR (NR) | < 0.0001 (< 0.0001) | 42% (46%) |
| OS (median) | NR (NR) | NR (NR) | 0.9298 (0.7246) | -2% (11%) |
| TNLT (median) | 60.2 months (NR) | NR (NR) | <0.0001 (0.0003) | 39% (39%) |
| TNCT (median) | NR (NR) | NR (NR) | (0.0006) (0.0011) | 34% (40%) |
| ORR* | 60.7% (55.0%) | 79.0% (74.0%) | <0.0001# (< 0.0001) | OR=2.43 (OR =2.33) |
| Complete Response (CR/CRu) rate* | 52.7% (47.7%) | (66.8%) | <0.0001 (< 0.0001) | OR=2.34 [ (OR = 2.21) |

*At end of maintenance/observation; # p values from chi-squared test
Values in parentheses correspond to 25 months median observation time (primary analysis). Values outside of parentheses correspond to 48 months median observation time (updated analysis).
PFS: progression-free survival; EFS: event-free survival; OS: overall survival; TNLT: time to next anti-lymphoma treatment; TNCT: time to next chemotherapy treatment; ORR: overall response rate; NR: not reached at time of clinical cut-off, OR: odds ratio.

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/m$^2$ 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 randomized to both parts of the study. After a median observation time of 31 months for patients randomised to the induction phase, R-CHOP significantly improved the outcome of patients with relapsed/refractory follicular lymphoma when compared to CHOP (see Table 6).

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

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

[1)] Estimates were calculated by hazard ratios

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

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

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

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

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

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

The benefit of MabThera maintenance treatment was confirmed in all subgroups analysed, regardless of induction regimen (CHOP or R-CHOP) or quality of response to induction treatment (CR or PR) (table 7). MabThera maintenance treatment significantly prolonged median PFS in patients responding

to CHOP induction therapy (median PFS 37.5 months vs. 11.6 months, p< 0.0001) as well as in those responding to R-CHOP induction (median PFS 51.9 months vs. 22.1 months, p=0.0071). Although subgroups were small, MabThera maintenance treatment provided a significant benefit in terms of overall survival for both patients responding to CHOP and patients responding to R-CHOP, although longer follow-up is required to confirm this observation.

*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/m$^2$, doxorubicin 50 mg/m$^2$, vincristine 1.4 mg/m$^2$ up to a maximum of 2 mg on day 1, and prednisolone 40 mg/m$^2$/day on days 1-5) every 3 weeks for eight cycles, or MabThera 375 mg/m$^2$ 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 patients subgroups (gender, age, age adjusted IPI, Ann Arbor stage, ECOG, β2 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 HACA, 1.1 % (4 patients) were positive.

*Chronic lymphocytic leukaemia*

In two open-label randomized trials, a total of 817 previously untreated patients and 552 patients with relapsed/refractory CLL were randomized to receive either FC chemotherapy (fludarabine 25 mg/m$^2$, cyclophosphamide 250 mg/m$^2$, 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/m$^2$ during the first cycle one day prior to chemotherapy and at a dosage of 500 mg/m$^2$ on day 1 of each subsequent treatment cycle. Patients were excluded from the study in relapsed/refractory CLL if they had previously been treated with monoclonal antibodies or if they were refractory (defined as failure to achieve a partial remission for at least 6 months) to fludarabine or any nucleoside analogue. A total of 810 patients (403 R-FC, 407 FC) for the first-line study (Table 8a and Table 8b) and 552 patients (276 R-FC, 276 FC) for the relapsed/refractory study (Table 9) were analyzed for efficacy.
In the first-line study, after a median observation time of 48.1 months, the median PFS was 55 months in the R-FC group and 33 months in the FC group (p < 0.0001, log-rank test). The analysis of overall survival showed a significant benefit of R-FC treatment over FC chemotherapy alone (p = 0.0319, log-

rank test) (Table 8a). The benefit in terms of PFS was consistently observed in most patient subgroups analyzed according to disease risk at baseline (i.e. Binet stages A-C) (Table 8b).

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

| Efficacy Parameter | Kaplan-Meier Estimate of Median Time to Event (Months) | | | Risk Reduction |
|---|---|---|---|---|
| | FC (N = 409) | R-FC (N=408) | Log-Rank p value | |
| Progression-free survival (PFS) | 32.8 | 55.3 | <0.0001 | 45% |
| Overall Survival | NR | NR | 0.0319 | 27% |
| Event Free Survival | 31.3 | 51.8 | <0.0001 | 44% |
| Response rate (CR, nPR, or PR) | 72.6% | 85.8% | <0.0001 | n.a. |
| CR rates | 16.9% | 36.0% | <0.0001 | n.a. |
| Duration of response* | 36.2 | 57.3 | <0.0001 | 44% |
| Disease free survival (DFS)** | 48.9 | 60.3 | 0.0520 | 31% |
| Time to new treatment | 47.2 | 69.7 | <0.0001 | 42% |

Response rate and CR rates analysed using Chi-squared Test. NR: not reached; n.a.: not applicable
*: only applicable to patients achieving a CR, nPR, PR
**: only applicable to patients achieving a CR

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

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

CI: Confidence Interval

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

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

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

*Response rate and CR rates analysed using Chi-squared Test.*
*: only applicable to patients achieving a CR, nPR, PR; NR: not reached n.a. not applicable
**: only applicable to patients achieving a CR;

Results from other supportive studies using MabThera in combination with other chemotherapy regimens (including CHOP, FCM, PC, PCM, bendamustine and cladribine) for the treatment of previously untreated and/or relapsed/refractory CLL patients have also demonstrated high overall response rates with benefit in terms of PFS rates, albeit with modestly higher toxicity (especially myelotoxicity). These studies support the use of MabThera with any chemotherapy.
Data in approximately 180 patients pre-treated with MabThera have demonstrated clinical benefit (including CR) and are supportive for MabThera re-treatment.

*Paediatric population*
The European Medicines Agency has waived the obligation to submit the results of studies with MabThera in all subsets of the paediatric population with follicular lymphoma and chronic lymphocytic leukaemia. 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 randomized, controlled, double-blind, multicenter study (Study 1).

Study 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.

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

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

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

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

| | Outcome† | Placebo+MTX | MabThera+MTX (2 x 1000 mg) |
|---|---|---|---|
| Study 1 | | N= 201 | N= 298 |
| | ACR20<br>ACR50<br>ACR70 | 36 (18%)<br>11 (5%)<br>3 (1%) | 153 (51%)***<br>80 (27%)***<br>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: ***$p \leq 0.0001$

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 9). Similarly, a good to moderate European League Against Rheumatism (EULAR) response was achieved by significantly more MabThera treated patients treated with MabThera and methotrexate compared to patients treated with methotrexate alone (Table 10).

*Radiographic response*

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

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

**Table 11 Radiographic outcomes at 1 year (mITT population)**

| | Placebo+MTX | MabThera+MTX 2 × 1000 mg |
|---|---|---|
| **Study 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 randomized to placebo + MTX in Study 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 study 1 demonstrated significantly reduced progression of structural joint damage in patients receiving MabThera in combination with methotrexate compared to methotrexate alone as well as a significantly higher proportion of patients with no progression of joint damage over the 2 year period.

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

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

**Table 12 Physical Function and Quality of Life outcomes at week 24 in study 1**

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

† Outcome at 24 weeks
Significant difference from placebo at the primary time point: * p < 0.05, **p < 0.001 ***p ≤ 0.0001
MCID HAQ-DI ≥0.22, MCID SF-36 PHS >5.42, MCID SF-36 MHS >6.33

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

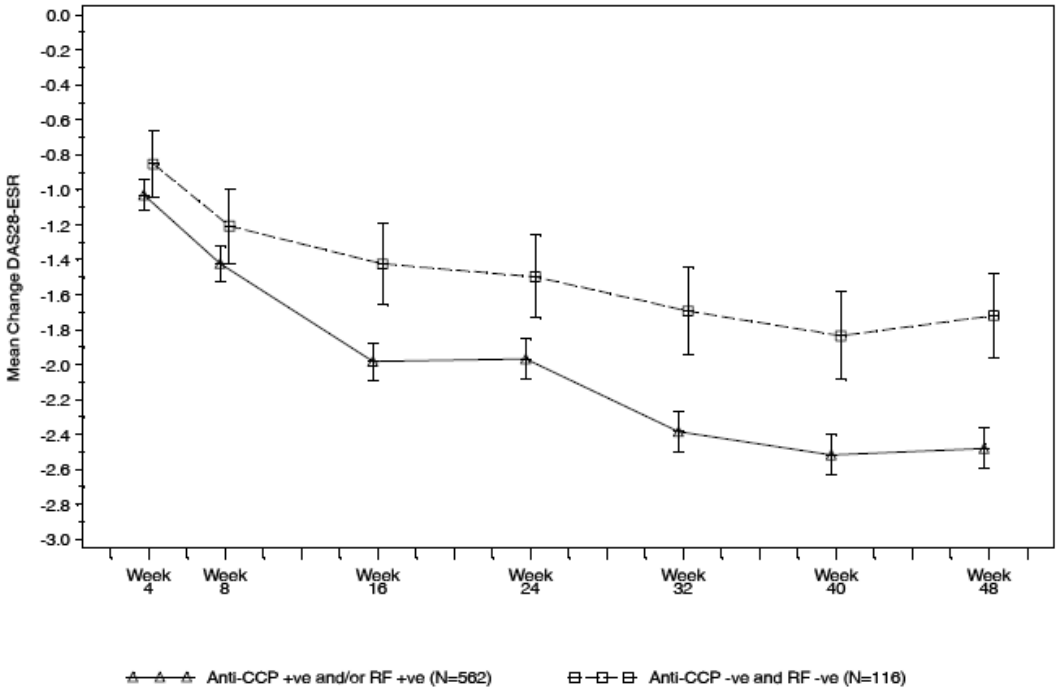
Efficacy outcomes in MabThera treated patients were analysed based on autoantibody status prior to commencing treatment. At Week 24, patients who were seropositive to RF and/or anti-CCP at baseline had a significantly increased probability of achieving ACR20 and 50 responses compared to seronegative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

**Table 13 Summary of efficacy by baseline autoantibody status**

| | Week 24 | | Week 48 | |
|---|---|---|---|---|
| | **Seropositive (n=514)** | **Seronegative (n=106)** | **Seropositive (n=506)** | **Seronegative (n=101)** |
| ACR20 (%) | 62.3* | 50.9 | 71. 1* | 51.5 |
| ACR50 (%) | 32.7* | 19.8 | 44.9** | 22.8 |
| ACR70 (%) | 12.1 | 5.7 | 20.9* | 6.9 |
| EULAR Response (%) | 74.8* | 62.9 | 84.3* | 72.3 |
| Mean change DAS28-ESR | -1.97** | -1.50 | -2.48*** | -1.72 |

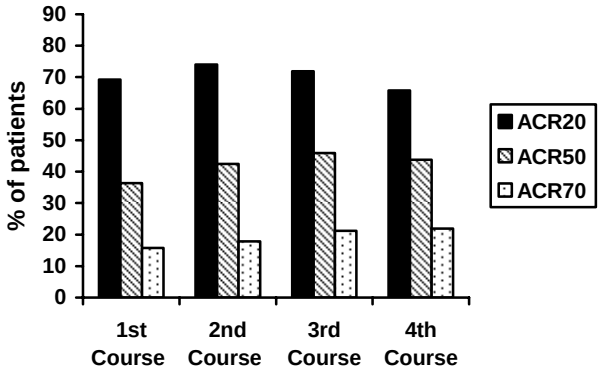
Significance levels were defined as ** p<0.05, **p<0.001, ***p<0.0001.*

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




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

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




*Clinical laboratory finding*
A total of 392/3095 (12.7%) patients with rheumatoid arthritis tested positive for HACA in clinical studies following therapy with MabThera. The emergence of HACA was not associated with clinical deterioration or with an increased risk of reactions to subsequent infusions in the majority of patients. The presence of HACA may be associated with worsening of infusion or allergic reactions after the second infusion of subsequent courses.

*Paediatric population*
The European Medicines Agency has waived the obligation to submit the results of studies with MabThera in all subsets of the paediatric population with autoimmune arthritis. See Section 4.2 for information on paediatric use.

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

A total of 197 patients aged 15 years or older with severely, active Granulomatosis with polyangiitis (75%) and Microscopic polyangiitis (24%) were enrolled and treated in an active-comparator, randomized, double-blind, multicenter, non-inferiority study.

Patients were randomized in a 1:1 ratio to receive either oral cyclophosphamide daily (2mg/kg/day) for 3-6 months or MabThera (375 mg/m$^2$) once weekly for 4 weeks. All patients in the cyclophosphamide arm received azathioprine maintenance therapy in during follow-up. Patients in both arms received 1000mg 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 study 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 study demonstrated non-inferiority of MabThera to cyclophosphamide for complete remission (CR) at 6 months (Table 14).

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

**Table 14 Percentage of 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%<br>95.1%[b] CI<br>(–3.2%, 24.3%) [a] |

– CI = confidence interval.
– * Worst case imputation
[a] Non-inferiority was demonstrated since the lower bound ( – 3.2%) was higher than the pre-determined non-inferiority margin ( – 20%).
[b] The 95.1% confidence level reflects an additional 0.001 alpha to account for an interim efficacy analysis.

**Table 15 Complete remission at 6-months by disease status**

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

Worst case imputation is applied for patients with missing data

*Complete Remission at 12 and 18 months*

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

*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 study preclude any conclusions regarding the efficacy of subsequent courses of MabThera in patients with Granulomatosis with polyangiitis and Microscopic polyangiitis.

Continued immunosuppressive therapy may be especially appropriate in patients at risk for relapses (i.e. with history of earlier relapses and Granulomatosis with polyangiitis, 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 in the study tested positive for HACA by 18 months. None of the 99 MabThera-treated patients were HACA positive at screening. The clinical relevance of HACA formation in MabThera-treated patients is unclear.

## 5.2 Pharmacokinetic properties

Non-Hodgkin's lymphoma

Based on a population pharmacokinetic analysis in 298 NHL patients who received single or multiple infusions of MabThera as a single agent or in combination with CHOP therapy (applied MabThera doses ranged from 100 to 500 mg/m$^2$), the typical population estimates of nonspecific clearance ($CL_1$), specific clearance ($CL_2$) likely contributed by B cells or tumor burden, and central compartment volume of distribution ($V_1$) were 0.14 l/day, 0.59 l/day, and 2.7 l, respectively. The estimated median terminal elimination half-life of MabThera was 22 days (range, 6.1 to 52 days). Baseline CD19-positive cell counts and size of measurable tumor lesions contributed to some of the variability in $CL_2$ of MabThera in data from 161 patients given 375 mg/m$^2$ as an intravenous infusion for 4 weekly doses. Patients with higher CD19-positive cell counts or tumor lesions had a higher $CL_2$. However, a large component of inter-individual variability remained for $CL_2$ after correction for CD19-positive cell counts and tumor lesion size. $V_1$ varied by body surface area (BSA) and CHOP therapy. This variability in $V_1$ (27.1% and 19.0%) contributed by the range in BSA (1.53 to 2.32 m$^2$) and concurrent CHOP therapy, respectively, were relatively small. Age, gender 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/m$^2$ 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/m$^2$ as an intravenous infusion at weekly intervals for 8 doses to 37 patients with NHL, the mean $C_{max}$ increased with each successive infusion, spanning from a mean of 243 µg/ml (range, 16 – 582 µg/ml) after the first infusion to 550 µg/ml (range, 171 – 1177 µg/ml) after the eighth infusion.

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

Chronic lymphocytic leukaemia

MabThera was administered as an IV infusion at a first-cycle dose of 375 mg/m$^2$ increased to 500 mg/m$^2$ each cycle for 5 doses in combination with fludarabine and cyclophosphamide in CLL patients. The mean $C_{max}$ (N=15) was 408 µg/ml (range, 97 – 764 µg/ml) after the fifth 500 mg/ m$^2$ 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 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 × 500 mg dose and ranged from 355 to 404 µg/ml for the 2 × 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 and Microscopic polyangiitis

Based on the population pharmacokinetic analysis of data in 97 patients with Granulomatosis with polyangiitis and Microscopic polyangiitis who received 375 mg/m$^2$ 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. The PK parameters of rituximab in these patients appear similar to what has been observed in rheumatoid arthritis patients.

## 5.3 Preclinical safety data

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

Developmental toxicity studies have been performed in cynomolgus monkeys at dosages 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 natally 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 immunization.

No long-term animal studies have been performed to establish the carcinogenic potential of rituximab, or to determine its effects on fertility in males or females. Standard tests to investigate mutagenicity have not been carried out, since such tests are not relevant for this molecule. However, due to its character it is unlikely that rituximab has any mutagenic potential.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sodium citrate
Polysorbate 80
Sodium chloride
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

30 months

The prepared infusion solution of MabThera is physically and chemically stable for 24 hours at 2 °C - 8 °C and subsequently 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

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

### 6.6 Special precautions for disposal and other handling

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

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 Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/067/001

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 2 June 1998
Date of latest renewal: 2 June 2008

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMA) http://www.ema.europa.eu/

## 1. NAME OF THE MEDICINAL PRODUCT

MabThera 500 mg concentrate for solution for infusion

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 10 mg of rituximab.

Each single-use vial containing 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.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear, colourless liquid.

## 4. CLINICAL PARTICULARS

MabThera is indicated in adults for the following indications:

### 4.1 Therapeutic indications

Non-Hodgkin's lymphoma (NHL)

MabThera is indicated for the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy.

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

MabThera monotherapy is indicated for treatment of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy.

MabThera is indicated for the treatment of patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy.

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

MabThera has been shown to reduce the rate of progression of joint damage as measured by x-ray and to improve physical function, when given in combination with methotrexate.

Granulomatosis with polyangiitis and Microscopic polyangiitis

MabThera, in combination with glucocorticoids, is indicated for the induction of remission in adult patients with severe, active Granulomatosis with polyangiitis (Wegener's) (GPA) and Microscopic polyangiitis (MPA).

## 4.2 Posology and method of administration

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

Posology

*Non-Hodgkin's lymphoma*

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

*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/m$^2$ 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/m$^2$ body surface area once every 2 months (starting 2 months after the last dose of induction therapy) until disease progression or for a maximum period of two years.

*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/m$^2$ body surface area once every 3 months (starting 3 months after the last dose of induction therapy) until disease progression or for a maximum period of two years.

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/m$^2$ 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/m$^2$ 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/m$^2$ body surface area, administered on day 1 of each chemotherapy cycle for 8 cycles after intravenous infusion of the glucocorticoid component of CHOP. Safety and efficacy of MabThera have not been established in combination with other chemotherapies in diffuse large B cell non-Hodgkin's lymphoma.

*Chronic lymphocytic leukaemia*

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

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

*Rheumatoid arthritis*

Patients treated with MabThera must be given the patient alert card with each infusion (see Annex IIIA – Labelling).

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.

Patients should receive treatment with 100 mg intravenous methylprednisolone to be completed 30 minutes prior to MabThera infusions to decrease the incidence and severity of infusion related reactions. Premedication consisting of an analgesic/anti-pyretic (e.g. paracetamol) and an anti-histaminic drug (e.g. diphenhydramine) should always be administered before each infusion of MabThera (see section 4.4).

The need for further courses should be evaluated 24 weeks following the previous course. Retreatment should be given at that time if residual disease activity remains, otherwise retreatment should be delayed until disease activity returns.

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

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

*Second infusion of each course*
Subsequent doses of MabThera can be infused at an initial rate of 100 mg/hr, and increased by 100 mg/hr increments at 30 minute intervals, to a maximum of 400 mg/hr.

*Granulomatosis with polyangiitis and Microscopic polyangiitis*

Patients treated with MabThera must be given the patient alert card with each infusion (see Annex IIIA – Labelling).

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

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

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 80mg/day, and tapered as rapidly as possible based on clinical need) during and after MabThera treatment.

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

Subsequent infusions (number 2 to 4): Subsequent infusions of MabThera can be started at a rate of 100 mg/h and increased by 100 mg/h increments every 30 minutes to a maximum of 400 mg/h.

Pneumocystis jiroveci pneumonia (PCP) prophylaxis is recommended for patients with Granulomatosis with polyangiitis or Microscopic polyangiitis during and following MabThera treatment, as appropriate.

*Special populations*

*Paediatric population*
The safety and efficacy of MabThera in children has not been established.

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

Method of administration

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

In Rheumatoid Arthritis, premedication with glucocorticoids should also be administered in order to reduce the frequency and severity of infusion-related reactions.

Premedication with glucocorticoids should be considered if MabThera is not given in combination with glucocorticoid-containing chemotherapy for treatment of non-Hodgkin’s lymphoma and chronic lymphocytic leukaemia.

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

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

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 (section 4.8) usually respond to a reduction in the rate of infusion. The infusion rate may be increased upon improvement of symptoms.

## 4.3 Contraindications

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

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

Active, severe infections (see section 4.4).

Patients in a severely immunocompromised state

Contraindications for use in Rheumatoid arthritis, Granulomatosis with polyangiitis and Microsccopic polyangiitis

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

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

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

Progressive multifocal leukoencephalopathy

All patients treated with MabThera for rheumatoid arthritis, Granulomatosis with polyangiitis and Microsccopic polyangiitis must be given the patient alert card with each infusion (see end of Annex IIIA - Labelling). The alert card contains important safety information for patients regarding potential increased risk of infections, including progressive multifocal leukoencephalopathy (PML).

Very rare cases of fatal PML have been reported following the 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, 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 reactions*
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 only 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.

***Severe cytokine release syndrome*** is characterised by severe dyspnea, 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, hyperphosphatemia, 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.

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 edema and acute reversible thrombocytopenia.

Since hypotension may occur during MabThera infusion, 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 x $10^9$/l and/or platelet counts < 75 x $10^9$/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 bemonitored 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.

*Immunizations*
The safety of immunization 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-randomized study, patients with relapsed low-grade NHL who received MabThera monotherapy when compared to healthy untreated controls had a lower rate of response to vaccination with tetanus recall antigen (16% vs. 81%) and Keyhole Limpet Haemocyanin (KLH) neoantigen (4% vs. 76% when assessed for >2-fold increase in antibody 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 titers 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, treatment should be permanently discontinued.

Rheumatoid arthritis, , Granulomatosis with polyangiitis and Microsccopic polyangiitis

*Methotrexate (MTX) naïve populations with Rheumatoid arthriitis*
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 (IRR), which may be related to release of cytokines and/or other chemical mediators. Premedication consisting of an analgesic/anti-pyretic drug and an anti-histaminic drug, should always be administered before each infusion of MabThera. In Reumatoid arthritis premedication with glucocorticoids should also be administered before each infusion of MabThera in order to reduce the frequency and severity of infusion-related reactions (see section 4.2 and section 4.8).

Severe infusion-related reactions 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 infusion-related reaction 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.

Infusion-related reactions for patients with Granulomatosis with polyangiitis and Microscopic polyangiitis were similar to those seen for Rheumatoid arthritis patients in clinical trials (see section 4.8).

*Cardiac disorders*
Angina pectoris, cardiac 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, Granulomatosis with polyangiitis and Microscopic polyangiitis patients receiving MabThera.

Hepatitis B virus (HBV) screening should be performed in all patientsbefore 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 guideline. 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, treatment should be permanently discontinued.

*Immunization*
Physicians should review the patient's vaccination status and follow current immunization guidelines prior to MabThera therapy. Vaccination should be completed at least 4 weeks prior to first administration of MabThera.

The safety of immunization 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 randomized study, patients with RA treated with MabThera and

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

In the overall experience of MabThera repeat treatment over one year in Rheumatoid arthritis, the proportions of patients with positive antibody titers 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. On the basis of limited experience with MabThera in rheumatoid arthritis patients (see section 4.8) the present data do not seem to suggest any increased risk of malignancy. However, the possible risk for the development of solid tumours cannot be excluded at this time.

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

In patients with rheumatoid arthritis, 283 patients received subsequent thereapy with a biologic DMARD following MabThera. In these patients the rate of clinically relevant infection while on MabThera was 6.01 per 100 patient years compared to 4.97 per 100 patients years following treatment with the biologic DMARD.

## 4.6 Fertility, pregnancy and lactation

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 MabTheraduring pregnancy. For these reasons MabThera should not be administered to pregnant women unless the possible benefit outweighs the potential risk.

Developmental toxicity studies performed in cynomolgus monkeys revealed no evidence of embryotoxicity in utero. New born offspring of maternal animals exposed to MabThera were noted to have depleted B cell populations during the post natal phase.

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

Breast-feeding
Whether rituximab is excreted in human milk is not known. However, because maternal IgG is excreted in human milk, and rituximab was detectable in milk from lactating monkeys, women should not breastfeed while treated with MabThera and for 12 months following MabThera treatment.

Fertility
There are no data currently available on the effects of MabThera on fertility.

## 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 events reported to date do not indicate that such an effect is likely.

## 4.8 Undesirable effects

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

The overall safety profile of MabThera in non-Hodgkin's lymphoma and chronic lymphocytic leukaemia is based on data from patients from clinical trials and from post-marketing surveillance. These patients were treated either with MabThera monotherapy (as induction treatment or maintenance treatment following induction treatment) or in combination with chemotherapy.

The most frequently observed adverse drug reactions (ADRs) in patients receiving MabThera were infusion-related reactions which occurred in the majority of patients during the first infusion. The incidence of infusion-related symptoms decreases substantially with subsequent infusions and is less than 1% after eight doses of MabThera.

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

The most frequent reported or observed serious adverse drug reactions were:
- Infusion-related reactions (including cytokine-release syndrome, tumour-lysis syndrome), 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.)

The frequencies of ADRs reported with MabThera alone or in combination with chemotherapy are summarised inTable 1. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1000) and very rare (< 1/10,000). 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**

| System Organ Class | Very Common | Common | Uncommon | Rare | Very Rare | Not known[8] |
|---|---|---|---|---|---|---|
| **Infections and infestations** | bacterial infections, viral infections, [+]bronchitis | sepsis, [+]pneumonia, [+]febrile infection, [+]herpes zoster, [+]respiratory tract infection, fungal infections, infections of unknown aetiology, [+]acute bronchitis, [+]sinusitis, hepatitis B[1] | | serious viral infection[2] Pneumocystis jirovecii | PML | |
| **Blood and lymphatic system disorders** | neutropenia, leucopenia, [+]febrile neutropenia, [+]thrombocytopenia | anaemia, [+]pancytopenia, [+]granulocytopenia | coagulation disorders, aplastic anaemia, haemolytic anaemia, lymphadenopathy | | transient increase in serum IgM levels[3] | late neutropenia[3] |
| **Immune system disorders** | infusion related reactions[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[8], loss of other senses[5] |
| **Eye disorders** | | lacrimation disorder, conjunctivitis | | | severe vision loss[5] | |
| **Ear and labyrinth disorders** | | tinnitus, ear pain | | | | hearing loss[5] |
| **Cardiac disorders** | | [+]myocardial infarction[4 and 6], arrhythmia, [+]atrial fibrillation, tachycardia, [+]cardiac disorder | [+]left ventricular failure, [+]supraventricular tachycardia, [+]ventricular tachycardia, [+]angina, [+]myocardial ischaemia, bradycardia | severe cardiac events [4 and 6] | heart failure[4 and 6] | |

| System Organ Class | Very Common | Common | Uncommon | Rare | Very Rare | Not known[8] |
|---|---|---|---|---|---|---|
| **Vascular disorders** | | hypertension, orthostatic hypotension, hypotension | | | vasculitis (predominately cutaneous), leukocytoclastic vasculiti | |
| **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 and bone disorders** | | hypertonia, myalgia, arthralgia, back pain, neck pain, pain | | | | |
| **Renal and urinary disorders** | | | | | renal failure[4] | |
| **General disorders and administration site conditions** | fever , chills, asthenia, headache | tumour pain, flushing, malaise, cold syndrome, [+]fatigue, [+]shivering, [+]multi-organ failure[4] | infusion site pain | | | |
| **Investigations** | decreased IgG levels | | | | | |

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

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

[2] see also section infection below

[3] see also section haematologic adverse reactions below

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

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

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

[7] includes fatal cases

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

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

*Infusion-related reactions*

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 events (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.

*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.

Localized candida infections as well as Herpes zoster was reported at a higher incidence in the MabThera-containing arm of randomized 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 hematopoetic 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 subjects 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 $1x10^9$/L between day 24 and 42 after the last dose) or occurred with a late onset (defined as neutrophil count below $1x10^9$/L later than 42 days after last dose in patients with no previous prolonged neutropenia or who recovered prior to day 42) following treatment with 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 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 ischemia) 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 events*
During the treatment period, 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 recognized 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-Hodgkgin 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 pediatric 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*
Older people (≥ 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*
Older people (≥ 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*

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 summarized 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. Events are listed in Table 2. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) and very rare (<1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The most frequent adverse reactions considered due to receipt of MabThera infusion related reactions. 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 forMabThera, 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 drug reactions reported in clinical trials or during postmarketing surveillance occurring in patients with rheumatoid arthritis receiving MabThera**

| System Organ Class | Very Common | Common | Uncommon | Rare | Very rare |
|---|---|---|---|---|---|
| **Infections and Infestations** | upper respiratory tract 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 |
| **Cardiac Disorders** | | | | Angina pectoris, atrial fibrillation, heart failure, myocardial infarction | Atrial flutter |
| **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, erythma) | | [3]Infusion related reactions (generalized oedema, bronchospasm, wheezing, laryngeal oedema, angioneurotic oedema, generalized pruritis, anaphylaxis, anaphylactoid reaction) | | |
| **General disorders and administration site conditions** | | | | | |
| **Metabolism and Nutritional Disorders** | | hypercholesterolemia | | | |
| **Nervous System disorders** | headache | paraesthesia, migraine, dizziness, sciatica | | | |
| **Skin and Subcutaneous Tissue Disorders** | | alopecia | | | Toxic Epidermal Necrolysis (Lyell's Syndrome), Stevens-Johnson Syndrome[5] |
| **Psychiatric Disorders** | | depression, anxiety | | | |
| **Gastrointestinal Disorders** | | dyspepsia, diarrhoea, gastro-oesophageal reflux, mouth ulceration, upper abdominal pain | | | |
| **Musculo skeletal 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. Infusion related reactions may occur as a result of hypersensitivity and/or to the mechanism of action.
[4] Includes observations collected as part of routine laboratory monitoring.
[5] Includes fatal cases

*Multiple courses*
Multiple courses of treatment are associated with a similar 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 infusion-related reactions (most frequent during the first treatment course), RA exacerbation and infections all of which were more frequent in the first 6 months of treatment.

*Infusion-related reactions*
The most frequent ADRs following receipt of MabThera in clinical studies were infusion-related reactions (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 decline with subsequent infusions. In clinical studies 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 studies. 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 section 4.2 and 4.4). Severe infusion-related reactions with fatal outcome have been reported in the post-marketing setting.

*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*
Serious cardiac events were reported at a rate of 1.3 per 100 patient years in the MabThera treated patients compared to 1.3 per 100 patient yearsin placebo treated patients. The proportions of patients experiencing cardiac events (all or serious) did not increase over multiple courses.

*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 MabTheratreated 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 pediatric 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 and Microscopic polyangiitis*

In the clinical study in Granulomatosis with polyangiitis and Microscopic polyangitis, 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 ≥ 5% in the MabThera group.

**Table 3. Adverse Drug Reactions occurring at 6-months in ≥ 5% of patients receiving MabThera, and at a higher frequency than the comparator group, in the pivotal clinical study**

| **Body System**<br><br>**Adverse event** | **Rituximab**<br><br>**(n=99)** |
|---|---|
| **Blood and lymphatic system disorders** | |
| Thrombocytopenia | 7% |
| **Gastrointestinal disorders** | |
| Diarrhoea | 18% |
| Dyspepsia | 6% |
| Constipation | 5% |
| **General disorders and administration site conditions** | |
| Peripheral oedema | 16% |
| **Immune system disorders** | |
| Cytokine release syndrome | 5% |

| **Body System**<br><br>**Adverse event** | **Rituximab**<br><br>**(n=99)** |
|---|---|
| **Infections and infestations** | |
| Urinary tract infection | 7% |
| Bronchitis | 5% |
| Herpes zoster | 5% |
| Nasopharyngitis | 5% |
| **Investigations** | |
| Decreased haemoglobin | 6% |
| **Metabolism and nutrition disorders** | |
| Hyperkalaemia | 5% |
| **Musculoskeletal and connective tissue disorders** | |
| Muscle spasms | 18% |
| Arthralgia | 15% |
| Back pain | 10% |
| Muscle weakness | 5% |
| Musculoskeletal pain | 5% |
| Pain in extremities | 5% |
| **Nervous system disorders** | |
| Dizziness | 10% |
| Tremor | 10% |

| **Body System**<br><br>**Adverse event** | **Rituximab**<br><br>**(n=99)** |
|---|---|
| **Psychiatric disorders** | |
| Insomnia | 14% |
| **Respiratory, thoracic and mediastinal disorders** | |
| Cough | 12% |
| Dyspnoea | 11% |
| Epistaxis | 11% |
| Nasal congestion | 6% |
| **Skin and subcutaneous tissue disorders** | |
| Acne | 7% |
| **Vascular disorders** | |
| Hypertension | 12% |
| Flushing | 5% |

**Further information on selected adverse drug reactions:**

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

*Infections:*
In the 99 MabThera patients, the overall rate of infection was approximately 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 Granulomatosis with polyangiitis and Microscopic polyangiitis clinical study was 2.00 per 100 patient years at the study common closing date (when the final patient had completed the follow-up period). On the basis of standardized

incidence ratios, the incidence of malignancies appears to be similar to that previously reported in patients with ANCA-associated vasculitis.

*Cardiovascular*
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).

*Hepatitis-B reactivation*
A small number of cases of hepatitis-B reactivation, some with fatal outcome, have been reported in Granulomatosis with polyangiitis and Microscopic polyangiitis patients receiving MabThera in the postmarketing setting.

*Hypogammaglobulinaemia*
Hypogammaglobulinaemia (IgA, IgG or IgM below the lower limit of normal) has been observed in Granulomatosis with polyangiitis and Microscopic polyangiitis patients treated with MabThera. At 6 months, in the active-controlled, randomized, double-blind, multicenter, non-inferiority study, 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. There was no increased rate in overall infections or serious infections in patients with low IgA, IgG or IgM.

*Neutropenia*
In the active-controlled, randomized, double-blind, multicenter, non-inferiority study of MabThera in Granulomatosis with polyangiitis and Microscopic polyangiitis, 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 Granulomatosis with polyangiitis and Microscopic polyangiitis 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.

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

## 4.9 Overdose

There has been no experience of overdose in human clinical trials. However, single doses higher than 1000 mg have not been tested in controlled clinical trials in patients with autoimmune disease. The highest dose tested to date is 5g in patients with chronic lymphocytic leukaemia. No additional safety signals were identified.

In the postmarketing setting five cases of MabTheraoverdose 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: 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 Fcγ 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 hematological 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 Granulomatosis with polyangiitis or Microscopic polyangiitis, the number of peripheral blood B cells decreased to <10 cells/µL after two weekly infusions of rituximab 375 mg/m$^2$, and remained at that level in most patients up to the 6 month timepoint. The majority of patients (81%) showed signs of B cell return, with counts >10 cells/µL by month 12, increasing to 87% of patients by month 18.

Clinical Experience in Non-Hodgkin's lymphoma and in chronic lymphocytic leukaemia

*Follicular lymphoma*

*Monotherapy*
Initial treatment, weekly for 4 doses
In the pivotal study, 166 patients with relapsed or chemoresistant low-grade or follicular B cell NHL received 375 mg/m$^2$ of MabThera as an intravenous infusion once weekly for four weeks. The overall response rate (ORR) in the intent-to-treat (ITT) population was 48 % ($CI_{95}$ % 41% - 56%) with a 6% complete response (CR) and a 42% partial response (PR) rate. The projected median time to progression (TTP) for responding patients was 13.0 months. In a subgroup analysis, the ORR was higher in patients with IWF B, C, and D histological subtypes as compared to IWF A subtype (58% vs. 12%), higher in patients whose largest lesion was < 5 cm vs. > 7 cm in greatest diameter (53% vs. 38%), and higher in patients with chemosensitive relapse as compared to chemoresistant (defined as duration of response < 3 months) relapse (50% vs. 22%). ORR in patients previously treated with autologous bone marrow transplant (ABMT) was 78% versus 43% in patients with no ABMT. Neither age, sex, lymphoma grade, initial diagnosis, presence or absence of bulky disease, normal or high LDH nor presence of extranodal disease had a statistically significant effect (Fisher's exact test) on response to MabThera. A statistically significant correlation was noted between response rates and bone marrow involvement. 40% of patients with bone marrow involvement responded compared to

59% of patients with no bone marrow involvement (p=0.0186). This finding was not supported by a stepwise logistic regression analysis in which the following factors were identified as prognostic factors: histological type, bcl-2 positivity at baseline, resistance to last chemotherapy and bulky disease.

Initial treatment, weekly for 8 doses
In a multi-centre, single-arm study, 37 patients with relapsed or chemoresistant, low grade or follicular B cell NHL received 375 mg/m$^2$ 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 studies, 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 study, 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/m$^2$ of MabThera as intravenous infusion weekly for four doses. Three of the patients had received two courses of MabThera before enrollment and thus were given a third course in the study. Two patients were re-treated twice in the study. For the 60 re-treatments on study, the ORR was 38% ($CI_{95}$ % 26% – 51%; 10% CR, 28% PR) with a projected median TTP for responding patients of 17.8 months (range 5.4 – 26.6). This compares favourably with the TTP achieved after the prior course of MabThera (12.4 months).

*Initial treatment, in combination with chemotherapy*
In an open-label randomised trial, a total of 322 previously untreated patients with follicular lymphoma were randomised to receive either CVP chemotherapy (cyclophosphamide 750 mg/m$^2$, vincristine 1.4 mg/m$^2$ up to a maximum of 2 mg on day 1, and prednisolone 40 mg/m$^2$/day on days 1 -5) every 3 weeks for 8 cycles or MabThera 375 mg/m$^2$ 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 center): 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 randomized 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 summarized in table 4.

**Table 4 Summary of key results from four phase III randomized 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 mo | OS rates, % |
|---|---|---|---|---|---|---|
| **M39021** | CVP, 159<br>R-CVP, 162 | 53 | 57<br>81 | 10<br>41 | Median TTP:<br>14.7<br>33.6<br>P<0.0001 | 53-months<br>71.1<br>80.9<br>p=0.029 |
| **GLSG'00** | CHOP, 205<br>R-CHOP, 223 | 18 | 90<br>96 | 17<br>20 | Median TTF: 2.6 years<br>Not reached<br>p < 0.001 | 18-months<br>90<br>95<br>p = 0.016 |
| **OSHO-39** | MCP, 96<br>R-MCP, 105 | 47 | 75<br>92 | 25<br>50 | Median PFS: 28.8<br>Not reached<br>p < 0.0001 | 48-months<br>74<br>87<br>p = 0.0096 |
| **FL2000** | CHVP-IFN, 183<br>R-CHVP-IFN, 175 | 42 | 85<br>94 | 49<br>76 | Median EFS: 36<br>Not reached<br>p < 0.0001 | 42-months<br>84<br>91<br>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-center, 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 randomized 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/m$^2$ body surface area given every 2 months until disease progression or for a maximum period of two years.

After a median observation time of 25 months from randomization, maintenance therapy with MabThera resulted in a clinically relevant and statistically significant improvement in the primary endpoint of investigator assessed progression-free survival (PFS) as compared to observation in patients with previously untreated follicular lymphoma (Table 5).

Significant benefit from maintenance treatment with MabThera was also seen for the secondary endpoints event-free survival (EFS), time to next anti-lymphoma treatment (TNLT) time to next chemotherapy (TNCT) and overall response rate (ORR) (Table 5). The results of the primary analysis were confirmed with longer follow-up (median observation time: 48 months), and have been added to Table 5 to show the comparison between the 25 and 48 month follow up periods.

**Table 5 Maintenance phase: overview of efficacy results MabThera vs. observation after 48 months median observation time (compared with results of primary analysis based on 25 months median observation time)**

| | Observation N=513 | MabThera N=505 | Log-rank P value | Risk reduction |
|---|---|---|---|---|
| **Primary Efficacy** | | | | |
| PFS (median) | 48.4 months (NR) | NR (NR) | <0.0001 (<0.0001) | 45% (50%) |
| **Secondary Efficacy** | | | | |
| EFS (median) | 47.6 months (37.8 months) | NR (NR) | <0.0001 (< 0.0001) | 42% (46%) |
| OS (median) | NR (NR) | NR (NR) | 0.9298 (0.7246) | -2% (11%) |
| TNLT (median) | 60.2 months (NR) | NR (NR) | <0.0001 (0.0003) | 39% (39%) |
| TNCT (median) | NR (NR) | NR (NR) | 0.0006 (0.0011) | 34% (40%) |
| ORR* | 60.7% (55.0%) | 79.0% (74.0%) | <0.0001# (< 0.0001) # | OR=2.43 (OR=2.33) |
| Complete Response (CR/CRu) rate* | 52.7% (47.7%) | 72.2% (66.8%) | < 0.0001# (< 0.0001) # | OR=2.34(OR=2.21) |

*At end of maintenance/observation; # p values from chi-squared test.
Values in parentheses correspond to 25 months median observation time (primary analysis). Values outside of parentheses correspond to 48 months median observation time (updated analysis).
PFS: progression-free survival; EFS: event-free survival; OS: overall survival; TNLT: time to next anti-lymphoma treatment; TNCT: time to next chemotherapy treatment; ORR: overall response rate; NR: not reached at time of clinical cut-off, OR: odds ratio

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/m$^2$ 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 randomized to both parts of the study. After a median observation time of 31 months for patients randomised to the induction phase, R-CHOP significantly improved the outcome of patients with relapsed/refractory follicular lymphoma when compared to CHOP (see Table 6).

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

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

[1)] Estimates were calculated by hazard ratios

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

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

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

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

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

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

The benefit of MabThera maintenance treatment was confirmed in all subgroups analysed, regardless of induction regimen (CHOP or R-CHOP) or quality of response to induction treatment (CR or PR) (table 7). MabThera maintenance treatment significantly prolonged median PFS in patients responding

to CHOP induction therapy (median PFS 37.5 months vs. 11.6 months, p< 0.0001) as well as in those responding to R-CHOP induction (median PFS 51.9 months vs. 22.1 months, p=0.0071). Although subgroups were small, MabThera maintenance treatment provided a significant benefit in terms of overall survival for both patients responding to CHOP and patients responding to R-CHOP, although longer follow-up is required to confirm this observation.

*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/m$^2$, doxorubicin 50 mg/m$^2$, vincristine 1.4 mg/m$^2$ up to a maximum of 2 mg on day 1, and prednisolone 40 mg/m$^2$/day on days 1-5) every 3 weeks for eight cycles, or MabThera 375 mg/m$^2$ 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 patients subgroups (gender, age, age adjusted IPI, Ann Arbor stage, ECOG, β2 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 HACA, 1.1 % (4 patients) were positive.

*Chronic lymphocytic leukaemia*

In two open-label randomized trials, a total of 817 previously untreated patients and 552 patients with relapsed/refractory CLL were randomized to receive either FC chemotherapy (fludarabine 25 mg/m$^2$, cyclophosphamide 250 mg/m$^2$, 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/m$^2$ during the first cycle one day prior to chemotherapy and at a dosage of 500 mg/m$^2$ on day 1 of each subsequent treatment cycle. Patients were excluded from the study in relapsed/refractory CLL if they had previously been treated with monoclonal antibodies or if they were refractory (defined as failure to achieve a partial remission for at least 6 months) to fludarabine or any nucleoside analogue. A total of 810 patients (403 R-FC, 407 FC) for the first-line study (Table 8a and Table 8b) and 552 patients (276 R-FC, 276 FC) for the relapsed/refractory study (Table 9) were analyzed for efficacy.

In the first-line study, after a median observation time of 48.1 months, the median PFS was 55 months in the R-FC group and 33 months in the FC group (p < 0.0001, log-rank test). The analysis of overall survival showed a significant benefit of R-FC treatment over FC chemotherapy alone (p = 0.0319, log-

rank test) (Table 8a). The benefit in terms of PFS was consistently observed in most patient subgroups analyzed according to disease risk at baseline (i.e. Binet stages A-C) (Table 8b).

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

| Efficacy Parameter | Kaplan-Meier Estimate of Median Time to Event (Months) | | | Risk Reduction |
|---|---|---|---|---|
| | FC (N = 409) | R-FC (N=408) | Log-Rank p value | |
| Progression-free survival (PFS) | 32.8 | 55.3 | <0.0001 | 45% |
| Overall Survival | NR | NR | 0.0319 | 27% |
| Event Free Survival | 31.3 | 51.8 | <0.0001 | 44% |
| Response rate (CR, nPR, or PR) | 72.6% | 85.8% | <0.0001 | n.a. |
| CR rates | 16.9% | 36.0% | <0.0001 | n.a. |
| Duration of response* | 36.2 | 57.3 | <0.0001 | 44% |
| Disease free survival (DFS)** | 48.9 | 60.3 | 0.0520 | 31% |
| Time to new treatment | 47.2 | 69.7 | <0.0001 | 42% |

Response rate and CR rates analysed using Chi-squared Test. NR: not reached; n.a.: not applicable
*: only applicable to patients achieving a CR, nPR, PR
**: only applicable to patients achieving a CR

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

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

CI: Confidence Interval

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

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

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

*Response rate and CR rates analysed using Chi-squared Test.*
*: only applicable to patients achieving a CR, nPR, PR; NR: not reached n.a. not applicable
**: only applicable to patients achieving a CR;

Results from other supportive studies using MabThera in combination with other chemotherapy regimens (including CHOP, FCM, PC, PCM, bendamustine and cladribine) for the treatment of previously untreated and/or relapsed/refractory CLL patients have also demonstrated high overall response rates with benefit in terms of PFS rates, albeit with modestly higher toxicity (expecially 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*
The European Medicines Agency has waived the obligation to submit the results of studies with MabTherain all subsets of the paediatric population with follicular lymphoma and chronic lymphocytic leukaemia. 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 randomized, controlled, double-blind, multicenter study (Study 1).

Study 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 MabTherabetween weeks 24 and 56, under an open label extension study protocol.

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

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

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

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

| | Outcome† | Placebo+MTX | MabThera+MTX (2 x 1000 mg) |
|---|---|---|---|
| Study 1 | | N= 201 | N= 298 |
| | ACR20<br>ACR50<br>ACR70 | 36 (18%)<br>11 (5%)<br>3 (1%) | 153 (51%)***<br>80 (27%)***<br>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: ***$p \leq 0.0001$

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 9). Similarly, in all studies a good to moderate European League Against Rheumatism (EULAR) response was achieved by significantly more MabThera treated patients treated with MabThera and methotrexate compared to patients treated with methotrexate alone (Table 10).

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

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

**Table 11 Radiographic outcomes at 1 year (mITT population)**

| | Placebo+MTX | MabThera +MTX 2 × 1000 mg |
|---|---|---|
| **Study 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 randomized to placebo + MTX in Study 1 received at least one course of RTX + MTX by one year
* p <0.05, ** p < 0.001. Abbreviation: NS, non siginficant

Inhibition of the rate of progressive joint damage was also observed long term. Radiographic analysis at 2 years in study 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) were observed in patients treated with MabThera compared to patients treated with methotrexate alone. The proportions of MabThera treated patients showing a minimal clinically important difference (MCID) in HAQ-DI (defined as an individual total score decrease of >0.22) was also higher than among patients receiving methotrexate alone (Table 12).

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

**Table 12 Physical Function and Quality of Life outcomes at week 24 in study 1**

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

† Outcome at 24 weeks
Significant difference from placebo at the primary time point: * p < 0.05, **p < 0.001 ***p ≤ 0.0001
MCID HAQ-DI ≥0.22, MCID SF-36 PHS >5.42, MCID SF-36 MHS >6.33

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

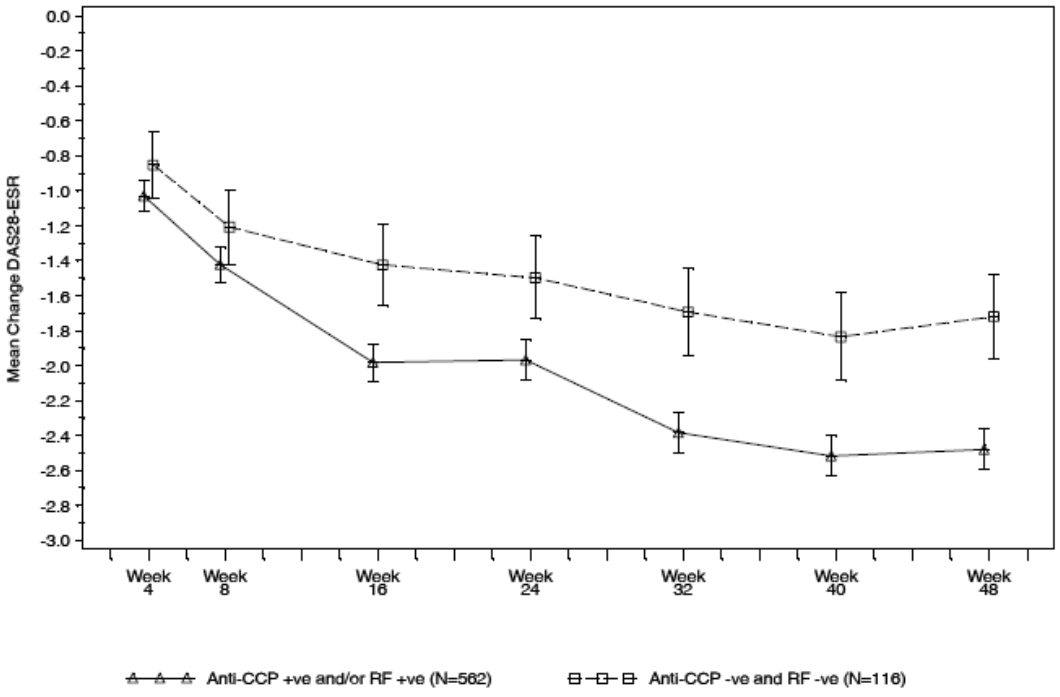
Efficacy outcomes in MabThera treated patients were analysed based on autoantibody status prior to commencing treatment. At Week 24, patients who were seropositive to RF and/or anti-CCP at baseline had a significantly increased probability of achieving ACR20 and 50 responses compared to seronegative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

**Table 13 Summary of efficacy by baseline autoantibody status**

| | Week 24 | | Week 48 | |
|---|---|---|---|---|
| | **Seropositive (n=514)** | **Seronegative (n=106)** | **Seropositive (n=506)** | **Seronegative (n=101)** |
| ACR20 (%) | 62.3* | 50.9 | 71. 1* | 51.5 |
| ACR50 (%) | 32.7* | 19.8 | 44.9** | 22.8 |
| ACR70 (%) | 12.1 | 5.7 | 20.9* | 6.9 |
| EULAR Response (%) | 74.8* | 62.9 | 84.3* | 72.3 |
| Mean change DAS28-ESR | -1.97** | -1.50 | -2.48*** | -1.72 |

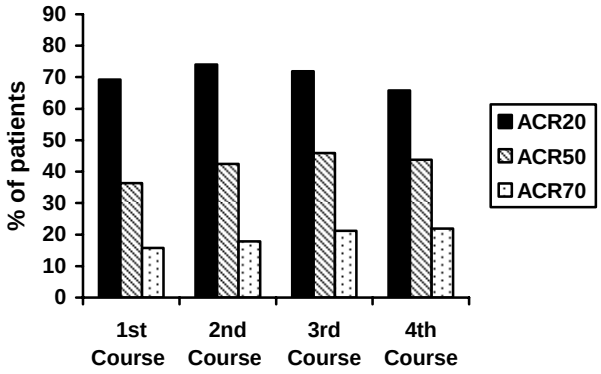
Significance levels were defined as * *p<0.05, **p<0.001, ***p<0.0001.*

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




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

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




*Clinical laboratory finding*
A total of 392/3095 (12.7%) patients with rheumatoid arthritis tested positive for HACA in clinical studies following therapy with MabThera. The emergence of HACA was not associated with clinical deterioration or with an increased risk of reactions to subsequent infusions in the majority of patients. The presence of HACA may be associated with worsening of infusion or allergic reactions after the second infusion of subsequent courses.

*Paediatric population*
The European Medicines Agency has waived the obligation to submit the results of studies with MabThera in all subsets of the paediatric population with autoimmune arthritis. See Section 4.2 for information on paediatric use.

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

A total of 197 patients aged 15 years or older with severely, active Granulomatosis with polyangiitis (75%) and Microscopic polyangiitis (24%) were enrolled and treated in an active-comparator, randomized, double-blind, multicenter, non-inferiority study.

Patients were randomized in a 1:1 ratio to receive either oral cyclophosphamide daily (2mg/kg/day) for 3-6 months or MabThera (375 mg/m$^2$) once weekly for 4 weeks. All patients in the cyclophosphamide arm received azathioprine maintenance therapy in during follow-up. Patients in both arms received 1000mg 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 study 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 study demonstrated non-inferiority of MabThera to cyclophosphamide for complete remission (CR) at 6 months (Table 14).

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

**Table 14 Percentage of 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%<br>95.1%[b] CI<br>(–3.2%, 24.3%) [a] |

– CI = confidence interval.
– * Worst case imputation
[a] Non-inferiority was demonstrated since the lower bound ( – 3.2%) was higher than the pre-determined non-inferiority margin ( – 20%).
[b] The 95.1% confidence level reflects an additional 0.001 alpha to account for an interim efficacy analysis.

**Table 15 Complete remission at 6-months by disease status**

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

Worst case imputation is applied for patients with missing data

*Complete Remission at 12 and 18 months*

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

*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 study preclude any conclusions regarding the efficacy of subsequent courses of MabThera in patients with Granulomatosis with polyangiitis and Microscopic polyangiitis.

Continued immunosuppressive therapy may be especially appropriate in patients at risk for relapses (i.e. with history of earlier relapses and Granulomatosis with polyangiitis, 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 in the study tested positive for HACA by 18 months. None of the 99 MabThera-treated patients were HACA positive at screening. The clinical relevance of HACA formation in MabThera-treated patients is unclear.

## 5.2 Pharmacokinetic properties

Non-Hodgkin's lymphoma

Based on a population pharmacokinetic analysis in 298 NHL patients who received single or multiple infusions of MabThera as a single agent or in combination with CHOP therapy (applied MabThera doses ranged from 100 to 500 mg/m$^2$), the typical population estimates of nonspecific clearance ($CL_1$), specific clearance ($CL_2$) likely contributed by B cells or tumor burden, and central compartment volume of distribution ($V_1$) were 0.14 l/day, 0.59 l/day, and 2.7 l, respectively. The estimated median terminal elimination half-life of MabThera was 22 days (range, 6.1 to 52 days). Baseline CD19-positive cell counts and size of measurable tumor lesions contributed to some of the variability in $CL_2$ of MabThera in data from 161 patients given 375 mg/m$^2$ as an intravenous infusion for 4 weekly doses. Patients with higher CD19-positive cell counts or tumor lesions had a higher $CL_2$. However, a large component of inter-individual variability remained for $CL_2$ after correction for CD19-positive cell counts and tumor lesion size. $V_1$ varied by body surface area (BSA) and CHOP therapy. This variability in $V_1$ (27.1% and 19.0%) contributed by the range in BSA (1.53 to 2.32 m$^2$) and concurrent CHOP therapy, respectively, were relatively small. Age, gender 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/m$^2$ 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/m$^2$ as an intravenous infusion at weekly intervals for 8 doses to 37 patients with NHL, the mean $C_{max}$ increased with each successive infusion, spanning from a mean of 243 µg/mL (range, 16 – 582 µg/ml) after the first infusion to 550 µg/ml (range, 171 – 1177 µg/ml) after the eighth infusion.

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

Chronic lymphocytic leukaemia

MabThera was administered as an IV infusion at a first-cycle dose of 375 mg/m$^2$ increased to 500 mg/m$^2$ each cycle for 5 doses in combination with fludarabine and cyclophosphamide in CLL patients. The mean $C_{max}$ (N=15) was 408 µg/mL (range, 97 – 764 µg/ml) after the fifth 500 mg/ m$^2$ 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 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 × 500 mg dose and ranged from 355 to 404 μg/ml for the 2 × 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 and Microscopic polyangiitis

Based on the population pharmacokinetic analysis of data in 97 patients with Granulomatosis with polyangiitis and Microscopic polyangiitis who received 375 mg/m$^2$ 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. The PK parameters of rituximab in these patients appear similar to what has been observed in rheumatoid arthritis patients.

## 5.3 Preclinical safety data

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

Developmental toxicity studies have been performed in cynomolgus monkeys at dosages 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 natally 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 immunization.

No long-term animal studies have been performed to establish the carcinogenic potential of rituximab, or to determine its effects on fertility in males or females. Standard tests to investigate mutagenicity have not been carried out, since such tests are not relevant for this molecule. However, due to its character it is unlikely that rituximab has any mutagenic potential.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sodium citrate
Polysorbate 80
Sodium chloride
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

30 months

The prepared infusion solution of MabThera is physically and chemically stable for 24 hours at 2 °C - 8 °C and subsequently 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

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.

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 Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/067/002

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 2 June 1998
Date of latest renewal: 2 June 2008

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMA) http://www.ema.europa.eu/

# ANNEX II

**A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Names and addresses of the manufacturers of the biological active substance

Genentech Inc.
1000 New Horizons Way
Vacaville, CA 95688
USA

Genentech, Inc.
1 Antibody Way
Oceanside, CA 92056 5802
USA

Name and address of the manufacturer responsible for batch release

Roche Pharma AG
Emil-Barell-Str. 1
D-79639 Grenzach-Wyhlen
Germany

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

## C OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) ) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines webportal.

## D CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2. of the Marketing Authorisation and any agreed and subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency.
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

An updated RMP shall be submitted by June 2013.

- **Additional risk minimisation measures**

The MAH must ensure that all physicians who are expected to prescribe MabThera are provided with the following:

Product information
Physician information
Patient information
Patient Alert card

The Physician information about MabThera should contain the following key elements:

- The need for close supervision during administration in an environment where full resuscitation facilities are immediately available
- The need to check, prior to MabThera treatment, for infections, for immunosuppression, for prior/current medication affecting the immune system and recent history of, or planned, vaccination
- The need to monitor patients for infections, especially PML, during and after MabThera treatment
- Detailed information on the risk of PML, the need for timely diagnosis of PML and appropriate measures to diagnose PML
- The need to advise patients on the risk of infections and PML, including the symptoms to be aware of and the need to contact their doctor immediately if they experience any.
- The need to provide patients with the Patient Alert Card with each infusion

The Patient information about MabThera should contain the following key elements:

- Detailed information on the risk of infections and PML
- Information on the signs and symptoms of infections, especially PML, and the need to contact their doctor immediately if they experience any
- The importance of sharing this information with their partner or caregiver
- Information on the Patient Alert Card

The Patient Alert Card for MabThera in non-oncology indications should contain the following key elements:

- The need to carry the card at all times and to show the card to all treating health care professionals
- Warning on the risk of infections and PML, including the symptoms
- The need for patients to contact their health care professional if symptoms occur

The Physician information, Patient information and Patient Alert Card must be agreed with the National Competent Authorities prior to distribution.

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

MabThera 100 mg concentrate for solution for infusion

Rituximab

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial contains 10 mg/ml rituximab.

## 3. LIST OF EXCIPIENTS

Sodium citrate, polysorbate 80, sodium chloride, sodium hydroxide, hydrochloric acid, water for injections.

## 4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
100 mg / 10 ml
2 vials of 10 ml

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after dilution
Read the package leaflet before use

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Keep the container in the outer carton, in order to protect from light

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/067/001

## 13. BATCH NUMBER

Batch

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**VIAL LABEL**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

MabThera 100 mg concentrate for solution for infusion

Rituximab

IV

## 2. METHOD OF ADMINISTRATION

For intravenous use after dilution

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Vial of 10 ml (10 mg/ml)
100 mg / 10 ml

## 6. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

MabThera 500 mg concentrate for solution for infusion

Rituximab

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial contains 10 mg/ml rituximab.

## 3. LIST OF EXCIPIENTS

Sodium citrate, polysorbate 80, sodium chloride, sodium hydroxide, hydrochloric acid, water for injections.

## 4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
500 mg / 50 ml
1 vial of 50 ml

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after dilution
Read the package leaflet before use

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Keep the container in the outer carton, in order to protect from light

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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AL7 1TW
United Kingdom

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/067/002

## 13. BATCH NUMBER

Batch

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**VIAL LABEL**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

MabThera 500 mg concentrate for solution for infusion

Rituximab

IV

## 2. METHOD OF ADMINISTRATION

For intravenous use after dilution

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Vial of 50 ml (10 mg/ml)
500 mg / 50 ml

## 6. OTHER

**PATIENT ALERT CARD TEXT FOR NON-ONCOLOGY INDICATIONS**

**<u>MABTHERA in Non-oncology indications</u>**
**<u>Patient Alert Card</u>**

This alert card contains important safety information that you need to be aware of before you are given MABTHERA and during treatment with MABTHERA.

- Show this card to any doctor involved in your treatment, not just your prescribing specialist physician

**Infections**

MABTHERA may increase the risk of getting infections.

Prior to MABTHERA treatment

- You should not be treated with MABTHERA if you have an active infection or serious problem with your immune system.
- TELL YOUR DOCTOR IF YOU ARE TAKING OR HAVE PREVIOUSLY TAKEN MEDICINES WHICH MAY AFFECT YOUR IMMUNE SYSTEM, SUCH AS CHEMOTHERAPY OR IMMUNOSUPPRESSIVE AGENTS

During or after treatment with MABTHERA

If you develop symptoms suggestive of infections, such as fever, persistent cough, weight loss, or listlessness, seek medical attention immediately.

Very rarely, some patients taking MabThera have had a serious brain infection called progressive multifocal leukoencephalopathy (PML) which has been fatal.

Symptoms of PML include memory loss, trouble thinking, difficulty with walking and/or loss of vision. You should **tell your doctor immediately if you experience any of these symptoms.**

**Dates of MABTHERA Treatment**:

Start:

_____

Most recent:

_____

- See the MABTHERA package leaflet for more information.
- Please make sure you also have a list of all your other medicines with you at any visit to a health care professional.

Patient's Name: _____

Doctor's Name: _____

Doctor's Phone: _____

- AS THE IMMUNOSUPRESSION CAUSED BY MABTHERA CAN LAST FOR SEVERAL MONTHS, SIDE EFFECTS MAY OCCUR EVEN AFTER YOU HAVE STOPPED TREATMENT. PLEASE THEREFORE KEEP THIS CARD WITH YOU FOR 24 MONTHS AFTER THE LAST DOSE OF MABTHERA,

# B. PACKAGE LEAFLET

**Package leaflet: Information for the patient**

**MabThera 100 mg concentrate for solution for infusion**
rituximab

**Read this leaflet carefully before you start taking this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet:**

1. What MabThera is and what it is used for
2. What you need to know before you use MabThera
3. How to use MabThera
4. Possible side effects
5. How to store MabThera
6. Contents of the pack and other information


## 1. What MabThera is and what it is used for

MabThera contains an antibody (rituximab) which is a type of protein. Rituximab binds to the surface of a type of white blood cell, the B lymphocyte. When rituximab binds to the surface of this cell it causes the cell to die.

MabThera may be used for the treatment of several different conditions. Your doctor may prescribe MabThera for the treatment of:

### a) Non-Hodgkin's Lymphoma
Non-Hodgkin's lymphoma is a disease of the lymphatic system. B lymphocytes are involved in the cause of some of the symptoms you may have. MabThera can be used alone or with other medicines your doctor may prescribe to induce remission of your disease. MabThera may be used as a continuous (maintenance) treatment for 2 years in patients who have responded to induction treatment.

### b) Chronic lymphocytic leukaemia
Chronic lymphocytic leukaemia (CLL) is the most common form of adult leukaemia. CLL affects a particular lymphocyte, the B cell, which originates from the bone marrow and develops in the lymph nodes. Patients with CLL have too many abnormal lymphocytes, which accumulate mainly in the bone marrow and blood. The proliferation of these abnormal B-lymphocytes is the cause of symptoms you may have. MabThera in combination with chemotherapy destroys these cells which are gradually removed from the body by biological processes.

### c) Rheumatoid arthritis
MabThera is used for the treatment of rheumatoid arthritis. Rheumatoid arthritis is a disease of the joints. B lymphocytes are involved in the cause of some of the symptoms you have. MabThera is used to treat rheumatoid arthritis in people who have already tried some other medicines which have either stopped working, have not worked well enough or have caused side effects. MabThera is usually taken together with another medicine called methotrexate.

MabThera slows down the damage to your joints caused by rheumatoid arthritis and improves your ability to do normal daily activities.

The best responses to MabThera are seen in those who have a positive blood test to rheumatoid factor (RF) and/or anti-Cyclic Citrullinated Peptide (anti-CCP). Both tests are commonly positive in rheumatoid arthritis and aid in confirming the diagnosis.

**d) Granulomatosis with polyangiitis or Microscopic polyangiitis**

MabThera is used for inducing remission in Granulomatosis with polyangiitis (formerly called Wegener's granulomatosis) or Microscopic polyangiitis,taken in combination with corticosteroids. Granulomatosis with polyangiitis and Microscopic polyangiitis are two forms of inflammation of the blood vessels which mainly affects the lungs and kidneys, but may affect other organs as well. B lymphocytes are involved in the cause of these conditions.

## 2. What you need to know before you use MabThera

**Do not take MabThera**
- if you are allergic to rituximab, to other similar proteins, or to any of the other ingredients of this medicine (listed in section 6)
- if you have an active, severe infection or have a severely decreased immune system function.
- if you have severe heart failure or severe uncontrolled heart disease and have Rheumatoid arthritis, Granulomatosis with polyangiitis or Microscopic polyangiitis.

If you are not sure about this, you should ask your doctor who will inform you accordingly.

**Tell your doctor before your MabThera treatment**
- if you think you have hepatitis infection now or have had it in the past. In a few cases, patients who have had hepatitis B might have a repeated attack of hepatitis, which can be fatal in very rare cases. Patients with a history of hepatitis B infection will be carefully checked by their doctor for signs of active hepatitis B.
- if you are taking treatment for high blood pressure. You may be asked not to take your medicines 12 hours before your infusion of MabThera. Some people have a fall in their blood pressure during the infusion.
- if you have ever had heart disease (i.e. angina, palpitations, or heart failure) or a history of breathing problems.
  Your doctor may need to take special care of you during your treatment with MabThera (in any of the above cases).

**Warnings and precautions**

Talk to your doctor, pharmacist or nurse before using MabThera
- tell your doctor if you are taking or have previously taken medicines which may affect your immune system, such as chemotherapy or immunosuppressive agents.

**If you have Rheumatoid arthritis, Granulomatosis with polyangiitis or Microscopic polyangiitis also tell your doctor**
- if you think you may have an infection, even a mild one like a cold. The cells that are affected by MabThera help to fight infection and you should wait until the infection has passed before you are given MabThera. Also please tell your doctor if you had a lot of infections in the past or suffer from severe infections.
- if you think you may need any vaccinations in the near future, including vaccinations needed to travel to other countries. Some vaccines should not be given at the same time as MabThera or in the months after you receive MabThera. Your doctor will check if you should have any vaccines before you receive MabThera.

At present, there is not very much information about MabThera treatment in children and adolescents; if you are under 18 years of age, you or your parent/carer should ask your doctor if MabThera is right for you.

**Other medicines and MabThera**
Before starting treatment, make sure your doctor knows if you are taking or have recently taken any other medicines (including those you have bought for yourself from a pharmacy, supermarket or health store). This is extremely important, as using more than one medicine at the same time can strengthen or weaken their effect. MabThera should not be used with other drugs unless your doctor has told you it is safe to do so.

**Pregnancy and breast-feeding**
You must tell your doctor if you are pregnant, if you think you are pregnant or if you intend to become pregnant. This is because MabThera is an antibody and can cross the placenta and affect your baby.

If you can get pregnant, you must use an effective method of birth control during therapy with MabThera and for 12 months after the last time you were treated with MabThera.

MabThera might also get into breast milk and so you should not breast-feed your baby during therapy with MabThera and for 12 months after the last time you were treated with MabThera

**Driving and using machines**
It is not known whether MabThera has an effect on your ability to drive a car or use machines.

## 3. How to use MabThera

MabThera is an infusion ("drip") which is given directly into your veins. You will be observed by a health care professional while you are being given MabThera in case you have any side effects during the infusion.
Before the infusion is given you will be given medicines to prevent or reduce possible reactions to MabThera.

**a) If you are being treated for non-Hodgkin's Lymphoma**
If you are treated with MabThera alone you will receive infusions at weekly intervals for a total of four infusions (days 1, 8, 15 and 22), so that the course of treatment usually lasts for 22 days. Repeated treatment courses with MabThera are possible. If you are treated with MabThera in combination with other medicines, you will receive an infusion of MabThera on the same day as the other medicines, which are usually given 8 times at 3-week intervals. If you have responded to treatment and are further treated with MabThera as continuous (maintenance) treatment, you will receive one infusion of MabThera every 2 or 3 months (as directed by your doctor) for two years. Your doctor may change the number of infusions depending on your disease.

**b) If you are being treated for chronic lymphocytic leukaemia**
When you are treated with MabThera in combination with chemotherapy, you will receive MabThera infusions on day 0 cycle 1 then day 1 of each cycle for 6 cycles in total. Each cycle has a duration of 28 days. The chemotherapy should be given after the MabThera infusion. Your doctor will decide if you should receive concomitant supportive therapy.

**c) If you are being treated for rheumatoid arthritis**
Each course of treatment is made up of two separate infusions which are given 2 weeks apart. Repeated courses of treatment with MabThera are possible. Depending on the signs and symptoms of your disease, your doctor will decide when you should receive more MabThera. This may be months from now.

**d) If you are being treated for Granulomatosis with polyangiitis or Microscopic polyangiitis**
Treatment with MabThera uses four separate infusions given at weekly intervals. Corticosteroids will usually be given by injection before the start of MabThera treatment. Corticosteroids given by mouth may be started at any time by your doctor to treat your condition.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Most side effects are mild to moderate but some may be serious and require treatment. Rarely, some of these reactions have been fatal.

**Infusion reactions**
During or within the first 2 hours of the first infusion you may develop fever, chills and shivering. Less frequently, some patients may experience pain at the infusion site, blisters, itching, sickness, tiredness, headache, breathing difficulties, tongue or throat swelling, itchy or runny nose, vomiting, flushing or palpitations, heart attack or low number of platelets. If you have heart disease or angina, these reactions might get worse. **Tell the person giving you the infusion immediately** if you develop any of these symptoms, as the infusion may need to be slowed down or stopped. You may require additional treatment such as an antihistamine or paracetamol. When these symptoms go away, or improve, the infusion can be continued. These reactions are less likely to happen after the second infusion. Your doctor may decide not to continue with MabThera treatment if you have a serious infusion reaction.

**Infections**
**Tell your doctor after your MabThera treatment** if you get any symptoms of an infection, for example fever, cough, sore throat, burning pain when passing urine, or you start to feel weak or generally unwell. You might get infections more easily following MabThera therapy. Often these are colds, but there have been cases of pneumonia or urinary infections.

Very rarely, some patients taking MabThera have had a serious brain infection, which has been fatal. **Tell your doctor immediately** if you have memory loss, trouble thinking, difficulty with walking or loss of vision.

If you are being treated for rheumatoid arthritis, you will also find this information in the Patient Alert Card you have been given by your doctor. It is important that you keep this Alert Card and show it to your partner or caregiver.

**Skin Reactions**
Very rarely, severe blistering skin conditions that can be life-threatening may occur. Redness, often associated with blisters, may appear on the skin or on mucous membranes, such as inside the mouth, the genital areas or the eyelids, and fever may be present. **Tell your doctor immediately if you experience any of these symptoms.**

**Other reactions**
**a) If you are being treated for non-Hodgkin's Lymphoma or chronic lymphocytic leukaemia**
The most commonly reported side effects due to MabThera (reported in more than 1 out of 10 patients) are:

- infections such as pneumonia (bacterial) and herpes (viral) or bronchial tube inflammation (bronchitis)
- low number of white blood cells, with or without fever, low number of platelets in the blood
- allergic reactions after infusion
- nausea
- skin rashes, itching, bald spots on the scalp, fever, chills, physical weakness, headache

- changes in laboratory tests carried out by your doctor. These include a decrease in the amount of some specific proteins in the blood (immunoglobulins) which help protect against infection.

Common side effects due to MabThera (reported in more than 1 out of 100 patients) include:

- infections such as sepsis and pneumonia (bacterial), herpes and hepatitis B (viral) or candidal (fungal) bronchial tube and sinuses inflammation, or other general infections of unknown origin
- low number of red blood cells, low number of red and white blood cells and platelets
- allergic reactions (hypersensitivity)
- high sugar level in the blood, weight loss, excess fluid in the face and the body, increased blood levels of the enzyme (LDH), low blood level of calcium
- abnormal sensations of the skin, such as numbness, tingling, pricking, burning, a creeping skin sensation, decreased sense of touch. Feeling restless, difficulty falling asleep, becoming red in the face and bruising of the skin as a consequence of dilation of the blood vessels, dizziness, anxiety
- an increased production of tears, secretion and shedding disorders, inflammation of the eye (conjunctivitis)
- ringing sound in the ears, ear pain
- heart disorders (heart attack, irregular heart rate, abnormally fast heart rate)
- high or low blood pressure, a decrease in blood pressure upon assuming an upright posture
- inflammation, irritation and / or tightness of the lungs, throat and / or sinuses, shortness of breath, too little oxygen reaching the body organs, coughing
- vomiting, diarrhoea, pain in the abdomen, irritation and /or ulceration of the throat and the mouth, difficulties in swallowing, constipation, indigestion. Eating disorders: decrease in the amount of food eaten with a consequential dangerous loss in weight
- skin disorders, burning sensation of the skin, itching, increased perspiration, night sweats
- musculoskeletal disorders**,** abnormal increase in tightness of muscle tone, pain, joint pain, muscle pain, back and neck pain
- general disorders, tumour pain, becoming markedly red in the face and other areas of the skin, general discomfort or uneasiness, flu syndrome, fatigue, shaking, multi-organ dysfunction

Uncommon side effects due to MabThera (reported in more than 1 out of 1000 patients) include:

- abnormal clotting, decrease of blood cells production, autoimmune decrease of red blood cells, swollen/enlarged lymph nodes
- low mood and loss of interest or pleasure in usual activities, nervousness
- taste changes
- heart disorder (heart attack, abnormally fast heart rate, reduced heart rate, irregular heart rate, chest pain) inflammation, irritation and/or tightness of the lungs, asthma, shortness of breath
- enlargement of the abdomen
- pain at the infusion site

Very rare side effects due to MabThera (reported in less than 1 out of 10,000 patients) include:

- temporary increased immunoglobulins, chemical disturbances in blood caused by the break-down of dying cancer cells, which can also lead to kidney failure
- nerve damage in arms and legs, paralysis of the face
- heart failure
- inflammation of blood vessels including those leading to skin symptoms
- perforation of the bowel wall
- kidney failure
- severe blistering skin conditions that can be life-threatening. Redness, often associated with blisters, may appear on the skin or on mucous membranes, such as inside the mouth, the genital areas or the eyelids, and fever may be present.
- Infection caused by a fungus called Pneumocystis jirovecii

Events occurring at a frequency not known:

- delayed reduction of white blood cells
- infusion-related immediate reduction of platelets (reversible), can be fatal in rare cases
- hearing loss
- loss of other senses

**b) If you are being treated for rheumatoid arthritis**

The most commonly reported side effects due to MabThera (reported in more than 1 out of 10 patients) are:

- Infections such as pneumonia (bacterial)
- Pain on passing water (urinary tract infection)
- Allergic reactions that are most likely to occur during an infusion, but can occur up-to 24-hours after infusion
- Changes in blood pressure, nausea, rash, fever, feeling itchy, runny or blocked nose and sneezing, shaking, rapid heart beat, and tiredness
- Headache
- Changes in laboratory tests carried out by your doctor. These include a decrease in the amount of some specific proteins in the blood (immunoglobulins) which help protect against infection.

Common side effects due to MabThera (reported in more than 1 out of 100 patients) include:

- Infections such as bronchial tube inflammation (bronchitis)
- A feeling of fullness or a throbbing pain behind the nose, cheeks and eyes (sinusitis), pain in the abdomen, vomiting and diarrhoea, breathing problems
- Fungal foot infection (athlete's foot)
- High cholesterol levels in the blood
- Abnormal sensations of the skin, such as numbness, tingling, pricking or burning, sciatica, migraine, dizziness
- Loss of hair
- Anxiety, depression
- Indigestion, diarrhoea, acid reflux, irritation and /or ulceration of the throat and the mouth
- Pain in the tummy, back, muscles and/or joints

Uncommon side effects due to MabThera (reported in more than 1 out of 1000 patients) include:

- Excess fluid retention in the face and body
- Inflammation, irritation and / or tightness of the lungs, and throat, coughing
- Skin reactions including hives, itching and rash
- Allergic reactions including wheezing or shortness of breath, swelling of the face and tongue, collapse

Very rare side effects due to MabThera (reported in less than 1 in 10,000 patients) include:

- A complex of symptoms occurring within a few weeks of an infusion of MabThera including allergic like reactions such as rash, itching, joint pain, swollen lymph glands and fever
- severe blistering skin conditions that can be life-threatening. Redness, often associated with blisters, may appear on the skin or on mucous membranes, such as inside the mouth, the genital areas or the eyelids, and fever may be present.

Other rarely-reported side-effects due to MabThera include a decreased number of white cells in the blood (neutrophils) that help to fight against infection. Some infections may be severe (please see information on ***Infections*** within this section).

**c) If you are being treated for granulomatosis with polyangiitis or microscopic polyangiitis**

The most commonly reported side effects due to MabThera (reported in more than 1 out of 10 patients) are:

- infections, such as chest infections, urinary tract infections (pain on passing water), colds and herpes infections
- allergic reactions that are most likely to occur during an infusion, but can occur up-to 24-hours after infusion
- diarrhoea
- coughing or shortness of breath
- nose bleeds
- raised blood pressure
- painful joints or back
- muscle twitches or shakiness
- feeling dizzy
- tremors (shakiness, often in the hands)
- difficulty sleeping (insomnia)
- swelling of the hands or ankles

Common side effects due to MabThera (reported in more than 1 out of 100 patients) include:

- indigestion
- constipation
- skin rashes, including acne or spots
- flushing or redness of the skin
- blocked nose
- tight or painful muscles
- pain in the muscles or in the hands or feet
- low number of red blood cells (anaemia)
- low numbers of platelets in the blood
- an increase in the amount of potassium in the blood
- changes in the rhythm of the heart, or the heart beating faster than normal

Very rare side effects due to MabThera (reported in less than 1 in 10,000 patients) include:

- severe blistering skin conditions that can be life-threatening. Redness, often associated with blisters, may appear on the skin or on mucous membranes, such as inside the mouth, the genital areas or the eyelids, and fever may be present.
- recurrence of a previous Hepatitis B infection

MabThera may also cause changes in laboratory tests carried out by your doctor. These include a decreased number of white cells in the blood (neutrophils) that help to fight against infection and a decrease in the amount of some specific proteins in the blood (immunoglobulins) which help protect against infection.
If you are receiving MabThera in combination with other medicines, some of the side effects you may experience may be due to the other medicine.

Reporting of side effects
If you get any side effects talk to your doctor, pharmacist or nurse. This includes any side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine

## 5. How to store MabThera

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.

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

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines that you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

### What MabThera contains

- The active ingredient in MabThera is called rituximab. The vial contains 100 mg of Rituximab (10 mg/ml).
- The other ingredients are sodium citrate, polysorbate 80, sodium chloride, sodium hydroxide, hydrochloric acid and water for injections.

### What MabThera looks like and contents of the pack

MabThera is a clear, colourless solution, supplied as a concentrate for solution for infusion. Vials of 10 ml are available as a pack of 2 vials.

### Marketing Authorisation Holder

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### Manufacturer

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**This leaflet was last revised in**

**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

**Package leaflet: Information for the patient**

**MabThera 500 mg concentrate for solution for infusion**
rituximab

**Read this leaflet carefully before you start taking this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet:**

1. What MabThera is and what it is used for
2. What you need to know before you use MabThera
3. How to use MabThera
4. Possible side effects
5. How to store MabThera
6. Contents of the pack and other information


## 1. What MabThera is and what it is used for

MabThera contains an antibody (rituximab) which is a type of protein. Rituximab binds to the surface of a type of white blood cell, the B lymphocyte. When rituximab binds to the surface of this cell it causes the cell to die.

MabThera may be used for the treatment of several different conditions. Your doctor may prescribe MabThera for the treatment of:

### a) Non-Hodgkin's Lymphoma
Non-Hodgkin's lymphoma is a disease of the lymphatic system. B lymphocytes are involved in the cause of some of the symptoms you may have. MabThera can be used alone or with other medicines your doctor may prescribe to induce remission of your disease. MabThera may be used as a continuous (maintenance) treatment for 2 years in patients who have responded to induction treatment.

### b) Chronic lymphocytic leukaemia
Chronic lymphocytic leukaemia (CLL) is the most common form of adult leukaemia. CLL affects a particular lymphocyte, the B cell, which originates from the bone marrow and develops in the lymph nodes. Patients with CLL have too many abnormal lymphocytes, which accumulate mainly in the bone marrow and blood. The proliferation of these abnormal B-lymphocytes is the cause of symptoms you may have. MabThera in combination with chemotherapy destroys these cells which are gradually removed from the body by biological processes.

### c) Rheumatoid arthritis
MabThera is used for the treatment of rheumatoid arthritis. Rheumatoid arthritis is a disease of the joints. B lymphocytes are involved in the cause of some of the symptoms you have. MabThera is used to treat rheumatoid arthritis in people who have already tried some other medicines which have either stopped working, have not worked well enough or have caused side effects. MabThera is usually taken together with another medicine called methotrexate.

MabThera slows down the damage to your joints caused by rheumatoid arthritis and improves your ability to do normal daily activities.

The best responses to MabThera are seen in those who have a positive blood test to rheumatoid factor (RF) and/or anti- Cyclic Citrullinated Peptide (anti-CCP). Both tests are commonly positive in rheumatoid arthritis and aid in confirming the diagnosis.

**d) Granulomatosis with polyangiitis or Microscopic polyangiitis**

MabThera is used for inducing remission in Granulomatosis with polyangiitis (formerly called Wegener's granulomatosis) or Microscopic polyangiitis, taken in combination with corticosteroids. Granulomatosis with polyangiitis and Microscopic polyangiitis are two forms of inflammation of the blood vessels which mainly affects the lungs and kidneys, but may affect other organs as well. B lymphocytes are involved in the cause of these conditions.

## 2. What you need to know before you use MabThera

**Do not take MabThera**

- if you are allergic to rituximab, to other similar proteins, or to any of the other ingredients of this medicine (listed in section 6)
- if you have an active, severe infection or have a severely decreased immune system function.
- if you have severe heart failure or severe uncontrolled heart disease and have Rheumatoid arthritis, Granulomatosis with polyangiitis or Microscopic polyangiitis.

If you are not sure about this, you should ask your doctor who will inform you accordingly.

**Tell your doctor before your MabThera treatment**

- if you think you have hepatitis infection now or have had it in the past. In a few cases, patients who have had hepatitis B might have a repeated attack of hepatitis, which can be fatal in very rare cases. Patients with a history of hepatitis B infection will be carefully checked by their doctor for signs of active hepatitis B.
- if you are taking treatment for high blood pressure. You may be asked not to take your medicines 12 hours before your infusion of MabThera. Some people have a fall in their blood pressure during the infusion.
- if you have ever had heart disease (i.e. angina, palpitations, or heart failure) or a history of breathing problems.
  Your doctor may need to take special care of you during your treatment with MabThera (in any of the above cases).

**Warnings and precautions**

Talk to your doctor, pharmacist or nurse before using MabThera

- tell your doctor if you are taking or have previously taken medicines which may affect your immune system, such as chemotherapy or immunosuppressive agents.

**If you have Rheumatoid arthritis, granulomatosis with polyangiitis or microscopic polyangiitis also tell your doctor**

- if you think you may have an infection, even a mild one like a cold. The cells that are affected by MabThera help to fight infection and you should wait until the infection has passed before you are given MabThera. Also please tell your doctor if you had a lot of infections in the past or suffer from severe infections.
- if you think you may need any vaccinations in the near future, including vaccinations needed to travel to other countries. Some vaccines should not be given at the same time as MabThera or in the months after you receive MabThera. Your doctor will check if you should have any vaccines before you receive MabThera.

At present, there is not very much information about MabThera treatment in children and adolescents; if you are under 18 years of age, you or your parent/carer should ask your doctor if MabThera is right for you.

**Other medicines and MabThera**
Before starting treatment, make sure your doctor knows if you are taking or have recently taken any other medicines (including those you have bought for yourself from a pharmacy, supermarket or health store). This is extremely important, as using more than one medicine at the same time can strengthen or weaken their effect. MabThera should not be used with other drugs unless your doctor has told you it is safe to do so.

**Pregnancy and breast-feeding**
You must tell your doctor if you are pregnant, if you think you are pregnant or if you intend to become pregnant. This is because MabThera is an antibody and can cross the placenta and affect your baby.

If you can get pregnant, you must use an effective method of birth control during therapy with MabThera and for 12 months after the last time you were treated with MabThera.

MabThera might also get into breast milk and so you should not breast-feed your baby during therapy with MabThera and for 12 months after the last time you were treated with MabThera

**Driving and using machines**
It is not known whether MabThera has an effect on your ability to drive a car or use machines.

## 3. How to use MabThera

MabThera is an infusion ("drip") which is given directly into your veins. You will be observed by a health care professional while you are being given MabThera in case you have any side effects during the infusion.

Before the infusion is given you will be given medicines to prevent or reduce possible reactions to MabThera.

**a) If you are being treated for non-Hodgkin's Lymphoma**
If you are treated with MabThera alone you will receive infusions at weekly intervals for a total of four infusions (days 1, 8, 15 and 22), so that the course of treatment usually lasts for 22 days. Repeated treatment courses with MabThera are possible. If you are treated with MabThera in combination with other medicines, you will receive an infusion of MabThera on the same day as the other medicines, which are usually given 8 times at 3-week intervals. If you have responded to treatment and are further treated with MabThera as continuous (maintenance) treatment, you will receive one infusion of MabThera every 2 or 3 months (as directed by your doctor) for two years. Your doctor may change the number of infusions depending on your disease.

**b) If you are being treated for chronic lymphocytic leukaemia**
When you are treated with MabThera in combination with chemotherapy, you will receive MabThera infusions on day 0 cycle 1 then day 1 of each cycle for 6 cycles in total. Each cycle has a duration of 28 days. The chemotherapy should be given after the MabThera infusion. Your doctor will decide if you should receive concomitant supportive therapy.

**c) If you are being treated for rheumatoid arthritis**
Each course of treatment is made up of two separate infusions which are given 2 weeks apart. Repeated courses of treatment with MabThera are possible. Depending on the signs and symptoms of your disease, your doctor will decide when you should receive more MabThera. This may be months from now.

**d) If you are being treated for granulomatosis with polyangiitis or microscopic polyangiitis**
Treatment with MabThera uses four separate infusions given at weekly intervals. Corticosteroids will usually be given by injection before the start of MabThera treatment. Corticosteroids given by mouth may be started at any time by your doctor to treat your condition.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Most side effects are mild to moderate but some may be serious and require treatment. Rarely, some of these reactions have been fatal.

**Infusion reactions**
During or within the first 2 hours of the first infusion you may develop fever, chills and shivering. Less frequently, some patients may experience pain at the infusion site, blisters, itching, sickness, tiredness, headache, breathing difficulties, tongue or throat swelling, itchy or runny nose, vomiting, flushing or palpitations, heart attack or low number of platelets. If you have heart disease or angina, these reactions might get worse. **Tell the person giving you the infusion immediately** if you develop any of these symptoms, as the infusion may need to be slowed down or stopped. You may require additional treatment such as an antihistamine or paracetamol. When these symptoms go away, or improve, the infusion can be continued. These reactions are less likely to happen after the second infusion. Your doctor may decide not to continue with MabThera treatment if you have a serious infusion reaction.

**Infections**
**Tell your doctor after your MabThera treatment** if you get any symptoms of an infection, for example fever, cough, sore throat, burning pain when passing urine, or you start to feel weak or generally unwell. You might get infections more easily following MabThera therapy. Often these are colds, but there have been cases of pneumonia or urinary infections.

Very rarely, some patients taking MabThera have had a serious brain infection, which has been fatal. **Tell your doctor immediately** if you have memory loss, trouble thinking, difficulty with walking or loss of vision.

If you are being treated for rheumatoid arthritis, you will also find this information in the Patient Alert Card you have been given by your doctor. It is important that you keep this Alert Card and show it to your partner or caregiver.

**Skin Reactions**
Very rarely, severe blistering skin conditions that can be life-threatening may occur. Redness, often associated with blisters, may appear on the skin or on mucous membranes, such as inside the mouth, the genital areas or the eyelids, and fever may be present. **Tell your doctor immediately if you experience any of these symptoms.**

**Other reactions**
**a) If you are being treated for non-Hodgkin's Lymphoma or chronic lymphocytic leukaemia**
The most commonly reported side effects due to MabThera (reported in more than 1 out of 10 patients) are:

- infections such as pneumonia (bacterial) and herpes (viral) or bronchial tube inflammation (bronchitis)
- low number of white blood cells, with or without fever, low number of platelets in the blood
- allergic reactions after infusion
- nausea
- skin rashes, itching ,bald spots on the scalp fever, chills, physical weakness, headache
- changes in laboratory tests carried out by your doctor. These include a decrease in the amount of some specific proteins in the blood (immunoglobulins) which help protect against infection.

Common side effects due to MabThera (reported in more than 1 out of 100 patients) include:

- infections such as sepsis and pneumonia (bacterial), herpes and hepatitis B (viral) or candidal (fungal) bronchial tube and sinuses inflammation, or other general infections of unknown origin
- low number of red blood cells, low number of red and white blood cells and platelets
- allergic reactions (hypersensitivity)
- high sugar level in the blood, weight loss, excess fluid in the face and the body, increased blood levels of the enzyme (LDH), low blood level of calcium
- abnormal sensations of the skin, such as numbness, tingling, pricking, burning, a creeping skin sensation, decreased sense of touch. Feeling restless, difficulty falling asleep, becoming red in the face and bruising of the skin as a consequence of dilation of the blood vessels, dizziness, anxiety
- an increased production of tears, secretion and shedding disorders, inflammation of the eye (conjunctivitis)
- ringing sound in the ears, ear pain
- heart disorders (heart attack, irregular heart rate, abnormally fast heart rate)
- high or low blood pressure, a decrease in blood pressure upon assuming an upright posture
- inflammation, irritation and / or tightness of the lungs, throat and / or sinuses, shortness of breath, too little oxygen reaching the body organs, coughing
- vomiting , diarrhoea, pain in the abdomen, irritation and /or ulceration of the throat and the mouth,difficulties in swallowing, constipation, indigestion. Eating disorders: decrease in the amount of food eaten with a consequential dangerous loss in weight
- skin disorders, burning sensation of the skin, itching, increased perspiration, night sweats
- musculoskeletal disorders**,** abnormal increase in tightness of muscle tone, pain, joint pain, muscle pain, back and neck pain
- general disorders, tumour pain, becoming markedly red in the face and other areas of the skin, general discomfort or uneasiness, flu syndrome, fatigue, shaking, multi-organ dysfunction

Uncommon side effects due to MabThera (reported in more than 1 out of 1000 patients) include:

- abnormal clotting, decrease of blood cells production, autoimmune decrease of red blood cells, swollen/enlarged lymph nodes
- low mood and loss of interest or pleasure in usual activities, nervousness
- taste changes
- heart disorder (heart attack, abnormally fast heart rate, reduced heart rate, irregular heart rate, chest pain) inflammation, irritation and/or thightness of the lungs, asthma, shortness of breath
- enlargement of the abdomen
- pain at the infusion site

Very rare side effects due to MabThera (reported in less than 1 out of 10,000 patients) include:

- temporary increased immunoglobulins, chemical disturbances in blood caused by the break-down of dying cancer cells, which can also lead to kidney failure
- nerve damage in arms and legs, paralysis of the face
- heart failure
- inflammation of blood vessels including those leading to skin symptoms
- perforation of the bowel wall
- kidney failure
- severe blistering skin conditions that can be life-threatening. Redness, often associated with blisters, may appear on the skin or on mucous membranes, such as inside the mouth, the genital areas or the eyelids, and fever may be present.
- Infection caused by a fungus called Pneumocystis jirovecii

Events occurring at a frequency not known:

- delayed reduction of white blood cells
- infusion-related immediate reduction of platelets (reversible), can be fatal in rare cases
- hearing loss
- loss of other senses

**b) If you are being treated for rheumatoid arthritis**

The most commonly reported side effects due to MabThera (reported in more than 1 out of 10 patients) are:

- Infections such as pneumonia (bacterial)
- Pain on passing water (urinary tract infection)
- Allergic reactions that are most likely to occur during an infusion, but can occur up-to 24-hours after infusion
- Changes in blood pressure, nausea, rash, fever, feeling itchy, runny or blocked nose and sneezing, shaking, rapid heart beat, and tiredness
- Headache
- Changes in laboratory tests carried out by your doctor. These include a decrease in the amount of some specific proteins in the blood (immunoglobulins) which help protect against infection.

Common side effects due to MabThera (reported in more than 1 out of 100 patients) include:

- Infections such as bronchial tube inflammation (bronchitis)
- A feeling of fullness or a throbbing pain behind the nose, cheeks and eyes (sinusitis), pain in the abdomen, vomiting and diarrhoea, breathing problems
- Fungal foot infection (athlete's foot)
- High cholesterol levels in the blood
- Abnormal sensations of the skin, such as numbness, tingling, pricking or burning, sciatica, migraine, dizziness
- Loss of hair
- Anxiety, depression
- Indigestion, diarrhoea, acid reflux, irritation and /or ulceration of the throat and the mouth
- Pain in the tummy, back, muscles and/or joints

Uncommon side effects due to MabThera (reported in more than 1 out of 1000 patients) include:

- Excess fluid retention in the face and body
- Inflammation, irritation and / or tightness of the lungs, and throat, coughing
- Skin reactions including hives, itching and rash
- Allergic reactions including wheezing or shortness of breath, swelling of the face and tongue, collapse

Very rare side effects due to MabThera (reported in less than 1 in 10,000 patients) include:

- A complex of symptoms occurring within a few weeks of an infusion of MabThera including allergic like reactions such as rash, itching, joint pain, swollen lymph glands and fever
- severe blistering skin conditions that can be life-threatening. Redness, often associated with blisters, may appear on the skin or on mucous membranes, such as inside the mouth, the genital areas or the eyelids, and fever may be present.

Other rarely-reported side-effects due to MabThera include a decreased number of white cells in the blood (neutrophils) that help to fight against infection. Some infections may be severe (please see information on ***Infections*** within this section).

**c) If you are being treated for granulomatosis with polyangiitis or microscopic polyangiitis**

The most commonly reported side effects due to MabThera (reported in more than 1 out of 10 patients) include:

- infections, such as chest infections, urinary tract infections (pain on passing water), colds and herpes infections
- allergic reactions that are most likely to occur during an infusion, but can occur up-to 24-hours after infusion
- diarrhoea
- coughing or shortness of breath
- nose bleeds
- raised blood pressure
- painful joints or back
- muscle twitches or shakiness
- feeling dizzy
- tremors (shakiness, often in the hands)
- difficulty sleeping (insomnia)
- swelling of the hands or ankles

Common side effects due to MabThera (reported in more than 1 out of 100 patients) include:

- indigestion
- constipation
- skin rashes, including acne or spots
- flushing or redness of the skin
- blocked nose
- tight or painful muscles
- pain in the muscles or in the hands or feet
- low number of red blood cells (anaemia)
- low numbers of platelets in the blood
- an increase in the amount of potassium in the blood
- changes in the rhythm of the heart, or the heart beating faster than normal

Very rare side effects due to MabThera (reported in less than 1 in 10,000 patients) include:

- severe blistering skin conditions that can be life-threatening. Redness, often associated with blisters, may appear on the skin or on mucous membranes, such as inside the mouth, the genital areas or the eyelids, and fever may be present.
- recurrence of a previous Hepatitis B infection

MabThera may also cause changes in laboratory tests carried out by your doctor. These include a decreased number of white cells in the blood (neutrophils) that help to fight against infection and a decrease in the amount of some specific proteins in the blood (immunoglobulins) which help protect against infection.

If you are receiving MabThera in combination with other medicines, some of the side effects you may experience may be due to the other medicine.

Reporting of side effects
If you get any side effects talk to your doctor, pharmacist or nurse. This includes any side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store MabThera

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.

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

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines that you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

### What MabThera contains

- The active ingredient in MabThera is called rituximab. The vial contains 500 mg of Rituximab (10 mg/ml).
- The other ingredients are sodium citrate, polysorbate 80, sodium chloride, sodium hydroxide, hydrochloric acid and water for injections.

### What MabThera looks like and contents of the pack

MabThera is a clear, colourless solution, supplied as a concentrate for solution for infusion. Pack of 1 vial.

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**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

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