NEW ZEALAND DATA SHEET
MabThera (rituximab)

1. PRODUCT NAME
MabThera (rituximab) concentrate for intravenous infusion 100mg

MabThera (rituximab) concentrate for intravenous infusion 500mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each mL contains 10 mg of rituximab.

Each 10 mL vial of MabThera 100mg concentrate for intravenous (IV) infusion contains 100 mg of rituximab.

Each 50 mL vial of MabThera 500mg concentrate for intravenous (IV) infusion contains 500 mg of rituximab.

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

Excipients with known effect
MabThera 100mg contains 2.3 mmol (52.6 mg) sodium per 10mL vial.

MabThera 500mg contains 11.5 mmol (263.2 mg) sodium per 50mL vial.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
MabThera concentrate for solution for intravenous (IV) infusion is a clear, colourless liquid supplied in sterile, preservative-free, non-pyrogenic single-dose vials.

4. CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Non-Hodgkin's lymphoma
MabThera is indicated for the treatment of patients with:
- CD20 positive, previously untreated low-grade or follicular, B-cell non-Hodgkin's lymphoma in combination with chemotherapy,
- CD20 positive, relapsed or chemoresistant low-grade or follicular, B-cell non-Hodgkin's lymphoma,
- CD20 positive diffuse large B-cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) chemotherapy.

MabThera is indicated for maintenance treatment of patients with CD20 positive, low grade or follicular, B-cell non-Hodgkin's lymphoma.

Chronic lymphocytic leukaemia
MabThera in combination with chemotherapy is indicated for the treatment of patients with chronic lymphocytic leukaemia (CLL).

Rheumatoid arthritis
MabThera in combination with methotrexate is indicated for the treatment of patients with severe active rheumatoid arthritis who have had an inadequate response or intolerance to other disease modifying agents.

Granulomatosis with polyangiitis (Wegener's) (GPA) and Microscopic polyangiitis (MPA)
MabThera in combination with glucocorticoids is indicated for the induction of remission in patients with severely active Granulomatosis with polyangiitis (GPA, also known as Wegener's granulomatosis) and Microscopic polyangiitis (MPA).

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

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

Haematology
Low-grade or follicular non-Hodgkin's lymphoma
Premedication consisting of an analgesic/anti-pyretic and an antihistamine agent should always be administered before each infusion of MabThera.

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

Initial treatment
The recommended dosage of MabThera used as monotherapy for adult patients is 375 mg/m^2 body surface area, administered as an IV infusion once weekly for 4 weeks.

The recommended dosage of MabThera in combination with any chemotherapy is 375 mg/m^2 body surface area per cycle for a total of:

- 8 cycles with R-CVP (cyclophosphamide, vincristine, prednisolone); 21 days/cycle.
- 8 cycles with R-MCP (mitoxantrone, chlorambucil, prednisolone); 28 days/cycle.
- 8 cycles with R-CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone); 21 days/cycle. 6 cycles if a complete remission is achieved after 4 cycles.
- 6 cycles with R-CHVP-interferon (cyclophosphamide, doxorubicin, etoposide, prednisolone); 21 days/cycle.

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

Re-treatment following relapse
Patients who have responded to MabThera initially have been treated again with MabThera at a dose of 375 mg/m^2 body surface area, administered as an IV infusion once weekly for 4 weeks (see sections 5.1 and 5.2).

Maintenance treatment

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

Relapsed/refractory patients after response to induction treatment may receive maintenance therapy with MabThera given at 375 mg/m^2 body surface area once every 3 months until disease progression or for a maximum period of two years (8 infusions).

Diffuse large B-cell non-Hodgkin's lymphoma

Premedication consisting of an analgesic/anti-pyretic and an antihistamine agent should always be administered before each infusion of MabThera.

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

MabThera should be used in combination with CHOP (cyclophosphamide, doxorubicin, prednisone and vincristine) chemotherapy. The recommended dosage of MabThera is 375 mg/m^2 body surface area, administered on day 1 of each chemotherapy cycle for 8 cycles after IV administration of the corticosteroid component of CHOP. The other components of CHOP should be given after the administration of MabThera.

Chronic lymphocytic leukaemia

Premedication consisting of an analgesic/anti-pyretic and an antihistamine agent should always be administered before each infusion of MabThera.

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

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 1 of the first treatment cycle followed by 500 mg/m^2 body surface area administered on day 1 of each subsequent cycle, for a total of 6 cycles (see section 5.1). The chemotherapy should be given after the infusion of MabThera.

Prophylaxis with adequate hydration and administration of uricostatics starting 48 hours prior to the start of therapy is recommended for CLL patients to reduce the risk of tumour lysis syndrome. CLL patients whose lymphocyte counts are > 25 x10^9/L have a higher risk of severe infusion-related reactions and should be treated with extreme caution. These patients should be very closely monitored during the first infusion. Consider use of a reduced infusion rate for the first infusion, or a split dosing over two days during the first cycle and any subsequent cycles if the lymphocyte count remains > 25 x 10^9/L. It is recommended to administer prednisone/prednisolone 100 mg IV shortly before infusion with MabThera to decrease the rate and severity of acute infusion reactions and/or cytokine release syndrome.

Infusion rates (non-Hodgkin's lymphoma and chronic lymphocytic leukaemia)

First infusion

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

Subsequent infusions

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

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 medicines should be applied.

Rheumatoid arthritis
Premedication consisting of an analgesic/anti-pyretic and an antihistamine agent should always be administered before each infusion of MabThera.

Premedication with glucocorticoids should also be administered in order to reduce the frequency and severity of infusion-related reactions. Patients should receive 100 mg IV methylprednisolone to be completed 30 minutes prior to each MabThera infusion (see section 4.4).

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

Patients may receive further courses of treatment, based on signs and symptoms of disease. In clinical studies, no patient received a second course of MabThera treatment within 16 weeks of the first infusion of the first course. The time interval between courses was variable, with the majority of patients receiving further therapy 6-12 months after the previous course. Some patients required even less frequent retreatment. The efficacy and safety of further courses is comparable to the first course (see sections 4.8 and 5.1).

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

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

Rheumatoid Arthritis Only; Alternative Subsequent, Faster, Infusion Schedule:
In RA, with a dose of 1000 mg MabThera, if there are no infusion related reactions or other reasons to slow or cease the infusion, the standard infusion schedules shown above result in an estimated duration of infusion of 4h 15 minutes for the first infusion and 3h 15 minutes for the subsequent infusions.

If patients do not experience a serious infusion related reaction with their first or subsequent infusions administered over the standard infusion schedule, a more rapid infusion can be administered for second and subsequent infusions using a concentration of 4 mg/mL in a 250 mL volume. Initiate at a rate of 250mg/h for the first 30 minutes and then 600 mg/h for the next 90 minutes. With this infusion schedule, the 1000mg/250mL infusion will generally be completed in 2 h. If the more rapid infusion is tolerated, this infusion schedule can be used when administering subsequent infusions.

Patients who have clinically significant cardiovascular disease, including arrhythmias, or previous serious infusion reactions to any prior biologic therapy or to MabThera, should not be administered the more rapid, 2 h, infusion.

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

Premedication consisting of an analgesic/anti-pyretic and an antihistamine should always be administered before each infusion of MabThera.

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

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

First infusion

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

Subsequent infusions

Subsequent infusions of MabThera can be administered 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 jirovecii pneumonia (PJP) prophylaxis is recommended for patients with GPA and MPA during and following MabThera treatment, as appropriate.

Special dosage instructions

Children and adolescents

The safety and effectiveness of MabThera in paediatric patients have not been established.

Elderly

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

Method of Administration

MabThera should be administered as an IV infusion through a dedicated line, in an environment where full resuscitation facilities are immediately available, and under the close supervision of an experienced healthcare professional.

MabThera intravenous formulation is not intended for subcutaneous (SC) administration. It is important to check the product labels to ensure that the appropriate formulation (IV or SC) is being given to the patient, as prescribed.

Do not administer the prepared infusion solutions as an IV push or bolus.

For instructions on dilution of the medicine before administration, see section 6.6

4.3 CONTRAINDICATIONS

MabThera is contraindicated in patients with known hypersensitivity to rituximab, to any excipients or to murine proteins.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

In order to improve traceability of biological medicinal products, the trade name of the administered product should be clearly recorded in the patient medical record.

Progressive multifocal leukoencephalopathy (PML)

Use of MabThera may be associated with an increased risk of progressive multifocal leukoencephalopathy (PML). Patients must be monitored for any new or worsening neurological symptoms or signs suggestive of PML. Physicians treating patients should consider PML in the differential diagnosis of patients reporting neurological symptoms and consultation with a neurologist should be considered as clinically indicated.

Physicians should be particularly alert to symptoms suggestive of PML that the patient may not notice (e.g. cognitive, neurological or psychiatric symptoms). If such symptoms occur, further administration of MabThera should be immediately suspended until a diagnosis of PML has been excluded. To establish or exclude a diagnosis of PML evaluation including MRI scan, CSF testing for JC viral DNA and repeat neurological assessments, should be considered. Once PML has been excluded, the administration of MabThera may resume.

If a diagnosis of PML is confirmed MabThera must be permanently discontinued. 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.

Non-Hodgkin's lymphoma and chronic lymphocytic leukaemia patients

Infusion-related Reactions

MabThera is associated with infusion-related reactions (IRRs), which may be related to release of cytokines and/or other chemical mediators. Cytokine release syndrome may be indistinguishable from acute hypersensitivity reactions. Severe IRRs with fatal outcome have been reported during post-marketing use. Severe IRRs usually manifested within 30 minutes to 2 hours after starting the first MabThera infusion, were characterised by pulmonary events and included, in some cases, rapid tumour lysis and features of tumour lysis syndrome in addition to fever, chills, rigors, hypotension, urticaria, angioedema and other symptoms (see section 4.8). Patients with a high tumour burden or with a high number ($> 25 \times 10^9$/L) of circulating malignant cells such as patients with CLL and mantle cell lymphoma may be at higher risk of developing severe IRRs. Infusion reaction symptoms are usually reversible with interruption of the infusion. Treatment of infusion-related symptoms with an anti-histamine and paracetamol is recommended. Additional treatment with bronchodilators or IV saline may be indicated. In most cases, the infusion can be resumed at a 50% reduction in rate (e.g. from 100 mg/h to 50 mg/h) when symptoms have completely resolved. Most patients who have experienced non-life threatening IRRs have been able to complete the full course of MabThera therapy. Further treatment of patients after complete resolution of signs and symptoms has rarely resulted in repeated severe IRRs.

Patients with a high number ($> 25 \times 10^9$/L) of circulating malignant cells or high tumour burden such as patients with CLL and mantle cell lymphoma, who may be at higher risk of especially severe IRRs, 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.

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

Pulmonary Events
Pulmonary events have included hypoxia, lung infiltration, and acute respiratory failure. Some of these events have been preceded by severe bronchospasm and dyspnoea. In some cases, symptoms worsened over time, while in others initial improvement was followed by clinical deterioration. Therefore, patients experiencing pulmonary events or other severe infusion-related symptoms should be closely monitored until complete resolution of their symptoms occurs. Patients with a history of pulmonary insufficiency or those with pulmonary tumour infiltration may be at greater risk of poor outcome and should be treated with increased caution. Acute respiratory failure may be accompanied by events such as pulmonary interstitial infiltration or oedema, visible on a chest x-ray. The syndrome usually manifests itself within 1 or 2 hours of initiating the first infusion. Patients who experience severe pulmonary events should have their infusion interrupted immediately (see section 4.2) and should receive aggressive symptomatic treatment.

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

Cardiovascular
Since hypotension may occur during MabThera infusion, consideration should be given to withholding antihypertensive medications 12 hours prior to and throughout MabThera infusion. Angina pectoris, cardiac arrhythmia, such as atrial flutter and fibrillation, heart failure and myocardial infarction have occurred in patients treated with MabThera. Therefore, patients with a history of cardiac disease should be monitored closely.

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

Consideration should be given to the need for regular full blood counts, including platelet counts, during monotherapy with MabThera. When MabThera is given in combination with

CHOP or CVP chemotherapy, regular full blood counts should be performed according to usual medical practice.

Infections
MabThera treatment should not be initiated in patients with severe active infections.

Hepatitis B Infections
Cases of hepatitis B (HB) reactivation including reports of fulminant hepatitis, some of which were fatal, have been reported in subjects receiving MabThera, although the majority of these subjects were also exposed to cytotoxic chemotherapy. The reports are confounded by both the underlying disease state, and the cytotoxic chemotherapy.

Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with MabThera. At a minimum this should include HB surface antigen status and anti-HB core antibody status. These can be complemented with other appropriate markers as per local guidelines. Patients with active HB disease should not be treated with MabThera. Patients with positive HB serology should consult a liver disease specialist before the start of treatment and should be monitored and managed according to guidelines to prevent HB reactivation.

Progressive Multifocal Leucoencephalopathy
Cases of progressive multifocal leucoencephalopathy (PML) have been reported during 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 haematopoietic stem cell transplant. Physicians treating patients with NHL or CLL should consider PML in the differential diagnosis of patients reporting neurological symptoms and consultation with a Neurologist should be considered as clinically indicated.

Skin Reactions
Severe skin reactions such as toxic epidermal necrolysis and Stevens-Johnson syndrome, some with fatal outcome, have been reported (see section 4.8). If signs and symptoms suggestive of a severe skin reaction occur, with a suspected relationship to MabThera, treatment should be permanently discontinued.

Immunisation
The safety of immunisation with live viral vaccines following MabThera therapy has not been studied and vaccination with live viral vaccines is not recommended.

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

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

Rheumatoid arthritis (RA), Granulomatosis with polyangiitis (Wegener's) (GPA) and Microscopic polyangiitis (MPA)
The efficacy and safety of MabThera for the treatment of autoimmune diseases other than RA, GPA and MPA have not been established.

Infusion-related reactions
MabThera is associated with infusion-related reactions (IRRs), which may be related to release of cytokines and/or other chemical mediators. The most common symptoms are headache, pruritus, throat irritation, flushing, rash, urticaria, hypertension, and pyrexia.

For RA patients, premedication consisting of an analgesic/anti-pyretic medicine and an anti-histamine medicine should always be administered before each infusion of MabThera. Premedication with glucocorticoids should also be administered before each infusion of MabThera in order to reduce the frequency and severity of IRRs (see sections 4.2 and 4.8).

For RA patients, most infusion-related events reported in clinical trials were mild to moderate in severity. Fewer than 1% of patients experienced serious IRRs, with most of these reported during the first infusion of the first course (see section 4.8). Severe IRRs with fatal outcome have been reported in the post-marketing setting (see section 4.8). Closely monitor patients with pre-existing cardiac conditions and those who experienced prior cardiopulmonary adverse reactions. In general, the proportion of patients experiencing any infusion reaction was higher following the first infusion of any treatment course than following the second infusion. Subsequent MabThera infusions were better tolerated by patients than the initial infusion.

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, IV saline or bronchodilators, and glucocorticoids if required. Depending on the severity of the IRR and the required interventions, temporarily or permanently discontinue MabThera. In most cases, the infusion can be resumed at a 50% reduction in rate (e.g. from 100 mg/h to 50 mg/h) when symptoms have completely resolved.

Hypersensitivity Reactions/Anaphylaxis
Anaphylactic and other hypersensitivity reactions have been reported following the IV administration of proteins to patients. Medicinal products for the treatment of hypersensitivity reactions, e.g., adrenaline, antihistamines and glucocorticoids, should be available for immediate use in the event of an allergic reaction during administration of MabThera.

For GPA and MPA patients, IRRs were similar to those seen for RA patients in clinical trials (see section 4.8). For GPA and MPA patients, MabThera was given in combination with high doses of glucocorticoids (see section 4.2), which may reduce the incidence and severity of these events (see information for RA indication above).

Cardiovascular
Since hypotension may occur during MabThera infusion, consideration should be given to withholding anti-hypertensive medications 12 hours prior to the MabThera infusion.

Angina pectoris, cardiac arrhythmias such as atrial flutter and fibrillation heart failure 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 may have an increased risk of infection following MabThera therapy. MabThera should not be administered to patients with an active infection 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 (see section 4.8). Patients who develop infection following MabThera therapy should be promptly evaluated and treated appropriately.

Hepatitis B Infections

Cases of hepatitis B (HB) reactivation, including those with a fatal outcome, have been reported in RA, GPA and MPA patients receiving MabThera.

Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with MabThera. At a minimum this should include HB surface antigen status and anti-HB core antibody status. These can be complemented with other appropriate markers as per local guidelines. Patients with active HB disease should not be treated with MabThera. Patients with positive HB serology should consult a liver disease specialist before the start of treatment and should be monitored and managed according to guidelines to prevent HB reactivation.

Skin Reactions

Severe skin reactions such as toxic epidermal necrolysis and Stevens-Johnson syndrome, some with fatal outcome, have been reported (see section 4.8). If signs and symptoms suggestive of a severe skin reaction occur, with a suspected relationship to MabThera, treatment should be permanently discontinued.

Progressive Multifocal Leukoencephalopathy (PML)

Cases of PML have been reported following use of MabThera for the treatment of autoimmune diseases including RA, GPA and MPA. Fatal outcome has been reported in auto-immune indications. Several, but not all of the reported cases had potential risk factors for PML, including the underlying disease, long-term immunosuppressive therapy or chemotherapy. PML has also been reported in patients with autoimmune disease not treated with MabThera. Physicians treating patients with autoimmune diseases should consider PML in the differential diagnosis of patients reporting neurological symptoms and consultation with a neurologist should be considered as clinically indicated.

Immunisation

For patients treated with MabThera, physicians should review the patient’s vaccination status and patients should, if possible, be brought up-to-date with all immunisations in alignment with current immunisation guidelines prior to initiating MabThera therapy. Vaccination should be completed at least 4 weeks prior to first administration of MabThera.

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

Patients treated with MabThera may receive non-live vaccinations. However, response rates to non-live vaccines may be reduced. In a randomised 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 (34% vs 80%), when given at least 6 months after MabThera as compared to patients only receiving methotrexate. Should non-live vaccinations be required whilst receiving MabThera, these should be completed at least 4 weeks prior to commencing the next course of MabThera.

In the overall experience of MabThera repeat treatment in RA patients over one year, the proportions of patients with positive antibody titres against S. pneumoniae, influenza, mumps, rubella, varicella and tetanus toxoid were generally similar to the proportions at baseline.

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

Paediatric use
The safety and effectiveness of MabThera in paediatric patients have not been established.

Hypogammaglobulinaemia has been observed in paediatric patients treated with MabThera, in some cases severe and requiring long-term immunoglobulin substitution therapy. The consequences of long term B cell depletion in paediatric patients are unknown.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

At present, there are limited data on possible 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 were no apparent effects of fludarabine and cyclophosphamide on the pharmacokinetics of MabThera.

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

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

In the RA clinical trial program, 373 MabThera-treated patients received subsequent therapy with other DMARDs, of whom 240 received a biologic DMARD. In these patients the rate of serious infection while on MabThera (prior to receiving a biologic DMARD) was 6.1 per 100 patient years compared to 4.9 per 100 patient years following subsequent treatment with an alternative biologic DMARD.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy
IgG immunoglobulins are known to cross the placental barrier.

Women of childbearing age must employ effective contraceptive methods during and for 12 months after treatment with MabThera.

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.

B-cell levels in human neonates following maternal exposure to MabThera have not been studied in clinical trials. There are no adequate and well-controlled data from studies in pregnant women. However transient B-cell depletion and lymphocytopenia have been reported in some infants born to mothers exposed to rituximab during pregnancy. For these reasons MabThera should not be administered to pregnant women unless the possible benefit outweighs the potential risk.

Breast-feeding
It is not known whether rituximab is excreted in human breast milk. Given, however, that maternal IgG enters breast milk, MabThera should not be administered to nursing mothers.

Fertility
Animal studies did not reveal deleterious effects of rituximab on reproductive organs.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
No studies on the effect 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
Clinical trials
Experience from clinical trials in haemato-oncology
The frequencies of adverse drug reactions (ADRs) reported with MabThera alone or in combination with chemotherapy are summarised in the tables below and are based on data from clinical trials. These ADRs had either occurred in single arm studies or had occurred with at least a 2% difference compared to the control arm in at least one of the major randomised clinical trials. ADRs are added to the appropriate category in the tables below according to the highest incidence seen in any of the major clinical trials. Within each frequency grouping ADRs are listed in descending order of severity. Frequencies are defined as very common ≥ 1/10 (≥ 10%), common ≥ 1/100 to < 1/10 (≥ 1% to < 10%) and uncommon ≥ 1/1,000 to < 1/100 (≥ 0.1% to < 1%).

MabThera monotherapy/maintenance therapy
The ADRs in the table below are based on data from single-arm studies including 356 patients with low-grade or follicular lymphoma, treated with MabThera weekly as a single agent for the treatment or re-treatment of non-Hodgkin's lymphoma (see section 5.1). The table also contains ADRs based on data from 671 patients with follicular lymphoma who received MabThera as maintenance therapy for up to 2 years following response to initial induction with CHOP, R-CHOP, R-CVP or R-FCM (see section 5.1). The ADRs were reported up to 12 months after treatment with monotherapy and up to 1 month after treatment with MabThera maintenance.

Table 1 Summary of ADRs reported in patients with low-grade or follicular lymphoma receiving MabThera monotherapy (n=356) or MabThera maintenance treatment (n=671) in clinical trials

System Organ Class	Very Common (≥ 10%)	Common (≥ 1% - < 10%)	Uncommon (≥ 0.1% - < 1%)
Infections and infestations	bacterial infections, viral infections	sepsis, +pneumonia, +febrile infection, +herpes zoster, +respiratory tract infection, fungal infections, infections of unknown aetiology	
Blood and the lymphatic system disorders	neutropenia, leucopenia	anaemia , thrombocytopenia	coagulation disorders, transient aplastic anaemia, haemolytic anaemia, lymphadenopathy
Immune system disorders	angiooedema	hypersensitivity	
Metabolism and nutrition disorders		hyperglycaemia, weight decrease, peripheral oedema, face oedema, increased LDH, hypocalcaemia	
Psychiatric disorders			depression, nervousness
Nervous system disorders		paresthesia, hypoesthesia, agitation, insomnia, vasodilatation, dizziness, anxiety	dysgeusia
Eye disorders		lacrimation disorder, conjunctivitis	
Ear and labyrinth disorders		tinnitus, ear pain	
Cardiac disorders		+myocardial infarction, arrhythmia, +atrial fibrillation, tachycardia, +cardiac disorder	+left ventricular failure, +supraventricular tachycardia, +ventricular tachycardia, +angina, +myocardial ischaemia, bradycardia
Vascular disorders		hypertension , orthostatic hypotension, hypotension	
Respiratory, thoracic and mediastinal disorders		bronchospasm, respiratory disease, chest pain, dyspnoea, cough, rhinitis	asthma, bronchiolitis obliterans, lung disorder, hypoxia
Gastrointestinal disorders	nausea	vomiting , diarrhoea, abdominal pain, dysphagia, stomatitis, constipation dyspepsia, anorexia, throat irritation	abdominal enlargement

System Organ Class	Very Common (≥ 10%)	Common (≥ 1% - < 10%)	Uncommon (≥ 0.1% - < 1%)
Skin and subcutaneous tissue disorders	pruritis, rash	urticaria, +alopecia, sweating, night sweats	
Musculoskeletal, connective tissue and bone disorders		hypertonia, myalgia, arthralgia, back pain, neck pain, pain	
General disorders and administration site conditions	fever, chills, asthenia, headache	tumour pain, flushing, malaise, cold syndrome	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 either trial is reported.

MabThera in combination with chemotherapy in non-Hodgkin's lymphoma and chronic lymphocytic leukaemia (CLL)

The ADRs listed in the table below are based on MabThera-arm data from controlled clinical trials that occurred in addition to those seen with monotherapy/maintenance therapy and/or at a higher frequency grouping: 202 patients with diffuse large B-cell lymphoma (DLBCL) treated with R-CHOP, from 234 and 162 patients with follicular lymphoma treated with R-CHOP or R-CVP, respectively, and from 397 previously untreated CLL patients and 274 relapsed/refractory CLL patients treated with MabThera in combination with fludarabine and cyclophosphamide (R-FC) (see section 5.1).

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

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

*includes reactivation and primary infections; frequency based on R-FC regimen in relapsed/refractory CLL
Frequency count was based on only severe reactions defined in clinical trials as ≥ Grade 3 NCI common toxicity criteria
Only the highest frequency observed in any trial is reported
#prolonged and/or delayed onset neutropenia after completion of an R-FC course in previously untreated or relapsed/refractory CLL

The following terms have been reported as adverse events, however, were reported at a similar (< 2% difference between the groups) or lower incidence in the MabThera-arms compared to control arms: haematotoxicity, neutropenic infection, urinary tract infection, septic shock, superinfection lung, implant infection, septicaemia staphylococcal, lung infection, rhinorrhoea, pulmonary oedema, cardiac failure, sensory disturbance, venous thrombosis, mucosal inflammation nos, influenza-like illness, oedema lower limb, abnormal

ejection fraction, pyrexia, general physical health deterioration, fall, multi-organ failure, venous thrombosis deep limb, positive blood culture, diabetes mellitus inadequate control.

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

Further information on selected, serious adverse drug reactions

Infusion-related reactions (IRRs)

Monotherapy - 4 weeks treatment

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

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

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

Infections

Monotherapy - 4 weeks treatment

MabThera induced B-cell depletion in 70% to 80% of patients but was associated with decreased serum immunoglobulins in only a minority of patients. Bacterial, viral, fungal and unknown etiology infections, irrespective of causal assessment, occurred in 30.3% of 356 patients. Severe infectious events (Grade 3/4), including sepsis occurred in 3.9% of patients.

Maintenance Treatment (NHL) up to 2 years

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

Data from clinical trials included cases of fatal PML in NHL patients that occurred after disease progression and retreatment (see section 4.4).

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

In the R-CVP study no increase in the frequency of infections or infestations was observed. The most common infections were upper respiratory tract infections which were reported for 12.3% patients on R-CVP and 16.4% patients receiving CVP. Serious infections were reported in 4.3% of the patients receiving R-CVP and 4.4% of the patients receiving CVP. No life-threatening infections were reported during this study.

In the R-CHOP study the overall incidence of Grade 2 to 4 infections was 45.5% in the R-CHOP group and 42.3% in the CHOP group. Grade 2 to 4 fungal infections were more frequent in the R-CHOP group (4.5% vs 2.6% in the CHOP group); this difference was due to a higher incidence of localised Candida infections during the treatment period. The incidence

of Grade 2 to 4 herpes zoster was higher in the R-CHOP group (4.5%) than in the CHOP group (1.5%). The proportion of patients with Grade 2 to 4 infections and/or febrile neutropenia was 55.4% in the R-CHOP group and 51.5% in the CHOP group.

In patients with CLL, the incidence of Grade 3/4 hepatitis B infection (reactivation and primary infection) was 2% R-FC vs 0% FC.

Haematologic Events
Monotherapy - 4 weeks treatment
Severe (Grade 3/4) neutropenia was reported in 4.2% of patients, severe anaemia was reported in 1.1% of patients and severe thrombocytopenia was reported in 1.7% of patients.

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

Combination Therapy (R-CVP in NHL; R-CHOP in DLBCL, R-FC in CLL)
During treatment with MabThera in combination with chemotherapy in clinical studies, Grade 3/4 leucopenia (R-CHOP 88% vs. CHOP 79%, R-FC 23% vs. FC 12%), neutropenia (R-CVP 24% vs. CVP 14%; R-CHOP 97% vs. CHOP 88%, R-FC 30% vs. FC 19% in previously untreated CLL), were usually reported with higher frequencies when compared to chemotherapy alone. However, the higher incidence of neutropenia in patients treated with MabThera and chemotherapy was not associated with a higher incidence of infections and infestations compared to patients treated with chemotherapy alone. Studies in previously untreated and relapsed/refractory CLL have established that in some cases neutropenia was prolonged or with a late onset following treatment in the MabThera plus FC group.

No relevant difference between the treatment arms was observed with respect to Grade 3/4 anaemia or thrombocytopenia. In the CLL first-line study, Grade 3/4 anaemia was reported by 4% of patients treated with R-FC compared to 7% of patients receiving FC, and Grade 3/4 thrombocytopenia was reported by 7% of patients in the R-FC group compared to 10% of patients in the FC group. In the relapsed/refractory CLL study, adverse events of Grade 3/4 anaemia were reported in 12% of patients treated with R-FC compared to 13% of patients receiving FC and Grade 3/4 thrombocytopenia was reported by 11% of patients in the R-FC group compared to 9% of patients in the FC group.

Cardiovascular Events
Monotherapy - 4 weeks treatment
Cardiovascular events were reported in 18.8% of patients during the treatment period. The most frequently reported events were hypotension and hypertension. Cases of Grade 3 or 4 arrhythmia (including ventricular and supraventricular tachycardia) and angina pectoris during a MabThera infusion were reported.

Maintenance Treatment (NHL) up to 2 years

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

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

In the R-CHOP study the incidence of Grade 3/4 cardiac arrhythmias, predominantly supraventricular arrhythmias such as tachycardia and atrial flutter/fibrillation, was higher in the R-CHOP group (6.9% of patients) as compared to the CHOP group (1.5% of patients). All of these 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 (see section 4.4). No difference between the R-CHOP and CHOP group was observed in the incidence of other Grade 3/4 cardiac events including heart failure, myocardial disease and manifestations of coronary artery disease.

In CLL, the overall incidence of Grade 3/4 cardiac disorders was low both in previously untreated patients (4% R-FC vs 3% FC) and in relapsed/refractory patients (4% R-FC vs 4% FC).

IgG Levels

Maintenance Treatment (NHL) up to 2 years

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

Neurologic Events

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

During the treatment period, 2% of patients in the R-CHOP group, all with cardiovascular risk factors, experienced thromboembolic cerebrovascular accidents during the first treatment cycle. There was no difference between the treatment groups in the incidence of other thromboembolic events. In contrast, 1.5% of patients had cerebrovascular events in the CHOP group, all of which occurred during the follow-up period.

In CLL, the overall incidence of Grade 3/4 nervous system disorders was low both in previously untreated patients (4% R-FC vs 4% FC) and in relapsed/refractory patients (3% R-FC vs 3% FC).

<u>Subpopulations</u>

Elderly patients (≥65 years)

Monotherapy - 4 weeks treatment

The incidence of any ADR and of Grade 3/4 ADRs was similar in elderly and younger patients (88.3% vs 92.0% for any ADR and 16.0% vs 18.1% for Grade 3/4 ADRs).

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

Bulky disease
Patients with bulky disease had a higher incidence of Grade 3/4 ADRs than patients without bulky disease (25.6% vs 15.4%). The incidence of any ADR was similar in these two groups (92.3% in bulky disease vs 89.2% in non-bulky disease).

Re-treatment with monotherapy
The percentage of patients reporting any ADR and Grade 3/4 ADRs upon re-treatment with further courses of MabThera was similar to the percentage of patients reporting any ADR and Grade 3/4 ADRs upon initial exposure (95.0% vs 89.7% for any ADR and 13.3% vs 14.8% for Grade 3/4 ADRs).

Experience from rheumatoid arthritis clinical trials
The safety profile of MabThera in the treatment of patients with moderate to severe RA is summarised in the sections below. In the all exposure population more than 3000 patients have received at least one treatment course and were followed for periods ranging from 6 months to over 5 years with an overall exposure equivalent to 7198 patient years; approximately 2300 patients received two or more courses of treatment during the follow up period.

The ADRs listed in Table 3 are based on data from placebo-controlled periods of four multicentre, RA clinical trials. The patient populations receiving MabThera differed between studies, ranging from early active RA patients who were methotrexate (MTX) naïve, through MTX inadequate responders (MTX-IR) to patients who had inadequate response to anti-TNF therapies (TNF-IR) (see section 5.1).

Patients received either 2 x 1000 mg or 2 x 500 mg of MabThera separated by an interval of two weeks, in addition to methotrexate (10-25 mg/week). The ADRs listed in Table 3 are those which occurred at a rate of at least 2%, with at least a 2% difference compared to the control arm and are presented regardless of dose. Frequencies in Table 3 and corresponding footnote are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1,000 to < 1/100).

Table 3: Summary of ADRs reported in patients with rheumatoid arthritis within control period of clinical trials †

System Organ Class	Very Common (≥ 10%)	Common (≥ 1% - < 10%)
Infections and Infestations	upper respiratory tract infection, urinary tract infection	bronchitis, sinusitis, gastroenteritis, tinea pedis
Immune System Disorders/ General disorders and administration site conditions	Infusion-related reactions	*infusion-related reactions: (hypertension, nausea, rash, pyrexia, pruritus, urticaria, throat irritation, hot flush, hypotension, rhinitis, rigors, tachycardia, fatigue,

System Organ Class	Very Common (≥ 10%)	Common (≥ 1% - < 10%)
		oropharyngeal pain, peripheral oedema, erythema)
Metabolism and Nutritional Disorders		hypercholesterolemia
Nervous System disorders	headache	paraesthesia, migraine, dizziness, sciatica,
Skin & Subcutaneous Tissue disorders		alopecia
Psychiatric Disorders		depression, anxiety
Gastrointestinal Disorders		dyspepsia, diarrhoea, gastro-oesophageal reflux, mouth ulceration, abdominal pain upper
Musculoskeletal and connective tissue disorders		arthralgia/musculoskeletal pain, osteoarthritis, bursitis

† This table includes all events with an incidence difference of ≥ 2% for MabThera compared to placebo. * In addition, medically significant events reported uncommonly associated with IRRs include: generalised oedema, bronchospasm, wheezing, laryngeal oedema, angioneurotic oedema, generalised pruritus, anaphylaxis and anaphylactoid reaction.

In the all exposure population, the safety profile was consistent with that seen in the controlled period of the clinical trials with no new ADRs identified.

Multiple courses
Multiple courses of treatment are associated with a similar ADR profile to that observed following first exposure. The safety profile improved with subsequent courses due to a decrease in IRRs, RA exacerbation and infections, all of which were more frequent in the first 6 months of treatment.

Further information on selected, serious adverse drug reactions

Infusion-related reactions (IRRs)
The most frequent ADRs following receipt of MabThera in clinical studies were IRRs. Among the 3095 patients treated with MabThera, 1077 (35%) experienced at least one IRR. The vast majority of IRRs were CTC Grade 1 or 2. In clinical studies fewer than 1% (14/3095 patients) of patients with RA who received an infusion of MabThera at any dose experienced a serious IRR. There were no CTC Grade 4 IRRs and no deaths due to IRRs in the clinical studies (see section 4.8). The proportion of CTC Grade 3 events, and of IRRs leading to withdrawal decreased by course and were rare from course 3 onwards.

Signs and/or symptoms suggesting an acute IRR (nausea, pruritis, fever, urticaria/rash, chills, pyrexia, rigors, sneezing, angioneurotic oedema, throat irritation, cough and bronchospasm, with or without associated hypotension or hypertension) were observed in 720/3095 (23%) patients following first infusion of the first exposure to MabThera. Premedication with IV glucocorticoid significantly reduced the incidence and severity of these events (see section 4.4).

In a study designed to evaluate the safety of a 120-minute MabThera infusion in patients with RA, patients with moderate-to-severe active RA who did not experience a serious infusion-related reaction (IRR) during or within 24 hours of their first studied infusion were allowed to receive a 120-minute infusion of MabThera IV. Patients with a history of a serious infusion reaction to a biologic therapy for RA were excluded from entry. The incidence, types and severity of infusion-related reactions (IRRs) were consistent with that observed historically. No serious IRRs were observed (see section 5.1).

Infections

The overall rate of infection was approximately 97 per 100 patient years in MabThera treated patients. The infections were predominantly mild to moderate and consisted mostly of upper respiratory tract infections and urinary tract infections. The rate of serious infections was approximately 4 per 100 patient years, some of which were fatal. In addition to the ADRs in Table 3, medically serious events reported also include pneumonia at a frequency of 1.9%.

Malignancies

The incidence of malignancy following exposure to MabThera in clinical studies (0.8 per 100 patient years) lies within the range expected for an age and gender matched population.

Laboratory Abnormalities

RA patients

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

Events of neutropenia associated with MabThera treatment, the majority of which were transient and mild or moderate in severity, were observed in clinical trials in RA patients after the first course of treatment. Neutropenia can occur several months after the administration of MabThera.

In placebo-controlled periods of clinical trials, 0.94% (13/1382) of MabThera treated patients and 0.27% (2/731) of placebo patients developed severe (Grade 3 or 4) neutropenia. In these studies, rates of severe neutropenia were 1.06 and 0.53/100 patient years after the first treatment course, respectively, and 0.97 and 0.88/100 patient years after multiple courses, respectively. Therefore, neutropenia can be considered an ADR for the first course only. Time to onset of neutropenia was variable. In clinical trials neutropenia was not associated with an observed increase in serious infection, and most patients continued to receive additional courses of MabThera after episodes of neutropenia.

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

In the GPA and MPA clinical study, 99 patients were treated with MabThera (375 mg/m^2, once weekly for 4 weeks) and glucocorticoids (see section 5.1). The ADRs listed in Table 4 were all adverse events which occurred at an incidence of ≥ 5% in the MabThera-treated group.

Table 4: Adverse Drug Reactions occurring in ≥ 5% of patients receiving MabThera, and at a higher frequency than cyclophosphamide, in the pivotal study at 6-months*

Adverse reactions	MabThera n =99	CYC n = 98
Blood and lymphatic system disorders		
Thrombocytopenia	7%	3%
Gastrointestinal disorders		
Diarrhoea	18%	12%
Dyspepsia	6%	5%
Constipation	5%	1%
General disorders and administration site conditions		
Peripheral oedema	16%	9%
Immune system disorders		
Infusion related reactions[a]	5%	2%
Infections and infestations		
Urinary tract infection	7%	3%
Bronchitis	5%	2%
Herpes zoster	5%	2%
Nasopharyngitis	5%	4%
Investigations		
Decreased haemoglobin	6%	4%
Metabolism and nutrition disorders		
Hypokalaemia	5%	2%
Musculoskeletal and connective tissue disorders		
Muscle spasm	18%	17%
Arthralgia	15%	10%
Back pain	10%	6%
Muscle weakness	5%	4%
Musculoskeletal pain	5%	0%
Pain in extremities	5%	3%
Nervous system disorders		
Dizziness	10%	9%
Tremor	10%	6%
Psychiatric disorders		
Insomnia	14%	13%
Respiratory, thoracic and mediastinal disorders		
Cough	12%	11%
Dyspnoea	11%	9%
Epistaxis	11%	6%
Nasal congestion	6%	2%
Skin and subcutaneous tissue disorders		
Acne	7%	5%
Vascular disorders		
Hypertension	12%	5%
Flushing	5%	4%

* The study design allowed for crossover or treatment by best medical judgment, and 13 patients in each treatment group received a second therapy during the 6-month study period. [a] Most common terms reported in the MabThera group included cytokine release syndrome, flushing, throat irritation, and tremor.

There was a higher incidence and rates of severe (Grade ≥ 3) and serious adverse events in older patients (aged ≥ 65 years) compared to younger patients (aged < 65 years), primarily attributable to anaemia and leucopenia, gastrointestinal disorders, and administrational site reactions. Deaths only occurred in older patients, with a similar incidence in the two treatment groups. Hospitalisations related to disease or study drug (per investigator's opinion) occurred more frequently in older patients in the MabThera group, with no hospitalisations occurring in older patients in the CYC group. There was no clear or consistent trend in the rates of infections and serious infections in younger patients versus older patients in either treatment group.

Patients with impaired renal function (glomerular filtration rate < 74.71 mL/min) at baseline had an increased risk of anaemia, infections (pneumonia, urinary tract infection), serious infections, death and hospitalisation, regardless of study treatment arm (MabThera or CYC).

Laboratory Abnormalities
Hypogammaglobulinaemia (IgA, IgG or IgM below the lower limit of normal) has been observed in GPA and MPA patients treated with MabThera. At 6 months, in the MabThera group, 27%, 58% and 51% of patients with normal Ig levels at baseline had low IgA, IgG and IgM levels, respectively compared to 25%, 50% and 46% in the CYC group. There was no increased rate in overall infections or serious infections in patients with low IgA, IgG or IgM.

In the active-controlled, randomised, double-blind, multicenter, non-inferiority study of MabThera in GPA and MPA, 24% of patients in the MabThera group (single course) and 23% of patients in the CYC group developed CTC grade 3 or greater neutropenia. Neutropenia was not associated with an observed increase in serious infection in MabThera-treated patients. The effect of multiple MabThera courses on the development of neutropenia in GPA and MPA patients has not been studied in clinical trials.

Further information on selected, serious adverse drug reactions

Infusion-related Reactions (IRRs)
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 IV glucocorticoids which may reduce the incidence and severity of these events.

Infections
In the 99 MabThera patients, the overall rate of infection was approximately 210 per 100 patient years (95% CI 173-256). Infections were predominately mild to moderate and consisted mostly of upper respiratory tract infections, herpes zoster and urinary tract infections. The rate of serious infections was approximately 25 per 100 patient years. The most frequently reported serious infection in the MabThera group was pneumonia at a frequency of 4%.

Malignancies
The incidence of malignancy in MabThera treated patients in the clinical study was 2.05 per 100 patient years. On the basis of standardised incidence ratios, this malignancy rate appears to be similar to rates previously reported in GPA and MPA populations.

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%).

Post-marketing experience
Non-Hodgkin's lymphoma and chronic lymphocytic leukaemia
The reporting frequencies in this section (rare, very rare) are based on estimated marketed exposures and largely data derived from spontaneous reports.

Additional cases of severe infusion-related reactions have been reported during post-marketing use of MabThera (see section 4.4).

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

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

Blood and lymphatic system: Rarely the onset of neutropenia has occurred more than four weeks after the last infusion of MabThera. Cases of infusion-related acute reversible thrombocytopenia have been reported. 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.

Respiratory system: Respiratory failure/insufficiency and lung infiltration in the context of infusion-related reactions (see section 4.4). In addition to pulmonary events associated with infusions, interstitial lung disease, some with fatal outcome, has been reported.

Skin and appendages: Severe bullous skin reactions including some fatal cases of toxic epidermal necrolysis and Stevens-Johnson syndrome have been reported rarely.

Nervous system: Cases of posterior reversible encephalopathy syndrome (PRES)/reversible posterior leukoencephalopathy syndrome (RPLS) have been reported. Signs and symptoms included visual disturbance, headache, seizures and altered mental status, with or without associated hypertension. A diagnosis of PRES/RPLS requires confirmation by brain imaging. The reported cases had recognised risk factors for PRES/RPLS, including the patients' underlying disease, hypertension, immunosuppressive therapy and/or chemotherapy. Cases of cranial neuropathy with or without peripheral neuropathy have been reported rarely. Signs and symptoms of cranial neuropathy, such as severe vision loss, hearing loss, loss of other senses and facial nerve palsy, occurred at various times up to several months after completion of MabThera therapy.

Body as a whole: Serum sickness-like reactions have been reported rarely.

Infections and infestations: Cases of hepatitis B reactivation, have been reported, the majority of which were in subjects receiving rituximab in combination with cytotoxic chemotherapy (see section 4.4). Other serious viral infections, either new, reactivation or exacerbation, some of which were fatal, have been reported with rituximab treatment. The majority of patients had received rituximab in combination with chemotherapy or as part of a haematopoietic stem cell transplant. Examples of these serious viral infections are infections caused by the herpes viruses (cytomegalovirus (CMV), Varicella zoster virus and Herpes simplex virus), JC virus (progressive multifocal leukoencephalopathy (PML) see section 4.4) and Hepatitis C virus. Progression of Kaposi's sarcoma has been observed in rituximab-exposed patients with pre-existing Kaposi's sarcoma. These cases occurred in non-approved indications and the majority of patients were HIV positive.

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

Rheumatoid arthritis
As part of the continuing post-marketing surveillance of MabThera safety, the following have been observed in the RA setting:

Infections and infestations: Progressive multifocal leukoencephalopathy (PML) and reactivation of hepatitis B infection have been reported.

Body as a whole: Serum sickness-like reaction has been reported.

Skin and subcutaneous tissue disorders: Toxic epidermal necrolysis and Stevens-Johnson syndrome, with fatal outcome in some cases, have been reported very rarely.

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

Nervous system: Cases of posterior reversible encephalopathy syndrome (PRES)/reversible posterior leukoencephalopathy syndrome (RPLS) have been reported. Signs and symptoms include visual disturbance, headache, seizures and altered mental status, with or without associated hypertension. A diagnosis of PRES/RPLS requires confirmation by brain imaging. The reported cases had recognised risk factors for PRES/RPLS, including hypertension, immunosuppressive therapy and/or other concomitant therapies.

General disorders and administration site conditions: Severe IRRs, some with fatal outcome, have been reported.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 OVERDOSE

Limited experience with doses higher than the approved intravenous doses of MabThera is available from clinical trials in humans. The highest intravenous dose tested to date is 5000 mg (2250 mg/m^2) tested in a dose escalation study in patients with chronic lymphocytic leukaemia. No additional safety signals were identified. Patients who experience overdose should have immediate interruption of their infusion and be closely monitored. Consideration should be given to the need for regular monitoring of blood cell count and for increased risk of infections while patients are B cell-depleted.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: antineoplastic agents, monoclonal antibodies, ATC code: L01X C02

Mechanism of Action

Rituximab is a chimeric mouse/human monoclonal antibody that binds specifically to the transmembrane antigen CD20. This antigen is located on pre-B- and mature B-lymphocytes, but not on haemopoietic stem cells, pro–B-cells, normal plasma cells or other normal tissue. The antigen is expressed on > 95% of all B–cell non-Hodgkin's lymphomas (NHLs). Following antibody binding, CD20 is not internalised or shed from the cell membrane into the environment. CD20 does not circulate in the plasma as a free antigen and, thus, does not compete for antibody binding.

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

Peripheral B–cell counts declined to levels below normal following the first dose of MabThera. In patients treated for haematological malignancies, B-cell recovery began within 6 months of treatment and generally returning to normal levels within 12 months after completion of therapy, although in some patients this may take longer (see section 4.8).

In patients with rheumatoid arthritis, the duration of peripheral B cell depletion was variable. The majority of patients received further treatment prior to full B cell repletion. A small proportion of patients had prolonged peripheral B cell depletion lasting 2 years or more after their last dose of MabThera.

In Granulomatosis with polyangiitis (Wegener's) (GPA) and Microscopic polyangiitis (MPA) patients, peripheral blood CD19 B-cells depleted to less than 10 cells/µl following the first two infusions of MabThera and remained at that level in most patients through month 6.

Of 67 patients evaluated for human anti-mouse antibody (HAMA), none were positive. Of 356 non-Hodgkin's lymphoma patients evaluated for human anti-chimeric antibody (HACA), 1.1% (4 patients) were positive.

Clinical trials

Low-grade or follicular non-Hodgkin's 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 IV infusion weekly for four doses. 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 histologic 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: histologic 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 IV infusion weekly for eight doses. The ORR was 57% ($CI_{95\%}$ 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/m^2 of MabThera as IV 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 IV infusion weekly for four doses. Three of the patients had received two courses of MabThera before enrolment and thus were given a third course in the study. Two patients were re-treated twice in the study. For the 60 re-treatments on study, the ORR was 38% ($CI_{95\%}$ 26% – 51%; 10% CR, 28% PR) with a projected median TTP for responding patients of 17.8 months (range 5.4 – 26.6). This compares favourably with the TTP achieved after the prior course of MabThera (12.4 months).

In combination with chemotherapy
Initial treatment
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 strong clinical benefit (p=0.029, log-rank test stratified by centre). Survival rates at 53 months were 80.9% for patients in the R-CVP group compared to 71.1% for patients in the CVP group.

Results from three other randomised trials using MabThera in combination with chemotherapy regimens other than CVP (CHOP, MCP, CHVP/interferon-alfa 2a) have also demonstrated significant improvements in response rates, time dependent parameters as well as in overall survival. Key results from all four studies are summarised in the table below.

Table 5: Summary of key results from four phase III randomised studies evaluating the benefit of MabThera with different chemotherapy regimens in follicular lymphoma

Study	Treatment, n	Median follow up, months	ORR, %	CR, %	Outcome[1] (months)	OS rates, %
M39021	CVP, 159 R-CVP, 162	53	57 81	10 41	Median TTP: 14.7 33.6 p<0.0001	71.1 80.9 p=0.029
GLSG'00	CHOP, 205 R-CHOP, 223	18	90 96	17 20	Median TTF: 31.2 Not reached p<0.001	90 95 p=0.016
OSHO-39	MCP, 96 R-MCP, 105	47	75 92	25 50	Median PFS: 28.8 Not reached p<0.0001	74 87 p=0.0096
FL2000	CHVP-IFN, 183 R-CHVP-IFN, 175	42	85 94	49 76	Median EFS: 36 Not reached p<0.0001	84 91 p=0.029

Abbreviations: ORR – overall response rate; CR – complete response; OS rates – overall survival rates at the time of the analyses; R – MabThera; CVP – cyclophosphamide, vincristine, prednisolone; CHOP - cyclophosphamide, doxorubicin, vincristine, prednisone; MCP – mitoxantrone, chlorambucil, prednisolone; CHVP - cyclophosphamide, doxorubicin, etoposide, prednisolone; IFN – interferon-alfa 2a. [1]M39021 outcome: TTP (time to progression or death); GLSG'00

outcomes: TTF (time to treatment failure); OSHO-39: PFS (progression free survival); FL2000 outcome: EFS (event free survival).

Maintenance therapy - previously untreated follicular NHL
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 randomised to MabThera maintenance therapy (n=505) or observation (n=513). The two treatment groups were well balanced with regards to baseline characteristics and disease status. MabThera maintenance treatment consisted of a single infusion of MabThera at 375 mg/m^2 body surface area given every two months until disease progression or for a maximum period of two years.

After a median observation time of 25 months from randomisation, 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 no maintenance therapy in patients with previously untreated follicular NHL (Table 6). This improvement in PFS was confirmed by an independent review committee (IRC).

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 6).

The updated analysis corresponding to a median observation time of 73 months from randomisation confirm the results of the primary analysis (Table 6).

Table 6: Overview of efficacy results for maintenance MabThera vs. observation (25 and 73 months' median observation time)

Efficacy Parameter	**Primary Analysis[a]**		**Updated Analysis[b]**	
	Observation N = 513	**MabThera Maintenance N = 505**	**Observation N = 513**	**MabThera Maintenance N = 505**
Primary Endpoint				
Progression-free Survival[c]				
Median time to event (months)	NR	NR	49	NR
p value (stratified log-rank test)	p < 0.0001		p < 0.0001	
HR [95% CI] (stratified)	0.50 [0.39;0.64]		0.58 [0.48;0.69]	
Secondary Endpoints				
Overall Survival				
Median time to event (months)	NR	NR	NR	NR
p value (stratified log-rank test)	p = 0.7246		p = 0.8959	
HR [95% CI] (stratified)	0.89 [0.45;1.74]		1.02 [0.71;1.47]	
Overall Response Rate at End of Maintenance/Observation				
Patients assessed at end of treatment	398	389	509	500
Responders (CR/Cru, PR)	219/398 (55%)	288/389 (74%)	309/509 (61%)	395/500 (79%)
p value (χ^2 test)	p < 0.0001		p < 0.0001	

Efficacy Parameter	Primary Analysis[a]		Updated Analysis[b]	
	Observation N = 513	**MabThera Maintenance N = 505**	**Observation N = 513**	**MabThera Maintenance N = 505**
Non-responders	179/398 (45%)	101/389 (26%)	200/509 (40%)	105/500 (21%)
Patients with complete response (CR/CRu)	190 (48%)	260 (67%)	268 (53%)	361 (72%)
partial response (PR)	29 (7%)	28 (7%)	41 (8%)	34 (7%)
stable disease (SD)	1 (<1%)	0 (0%)	1 (<1%)	1 (<1%)
progressive disease (PD)	162 (41%)	79 (20%)	181 (36%)	86 (17%)
Event-free Survival				
Median time to event (months)	38	NR	48	NR
p value (stratified log-rank test)	p < 0.0001		p < 0.0001	
HR [95% CI] (stratified)	0.54 [0.43;0.69]		0.61 [0.51;0.72]	
Time to Next Anti-Lymphoma Treatment				
Median time to event (months)	NR	NR	71	NR
p value (stratified log-rank test)	p = 0.0003		p < 0.0001	
HR [95% CI] (stratified)	0.61 [0.46;0.80]		0.63 [0.52;0.76]	
Time to Next Chemotherapy Treatment				
Median time to event (months)	NR	NR	85	NR
p value (stratified log-rank test)	p = 0.0011		p = 0.0006	
HR [95% CI] (stratified)	0.60 [0.44;0.82]		0.70 [0.57;0.86]	
Transformation Rate at First Progression				
Patients with progression	173	91	278	186
Patients with transformation	19/513 (4%)	11/505 (2%)	24/513 (5%)	16/505 (3%)

HR: hazard ratio; NR: not reached. 1 month = 30.4375 days (i.e., 365.25 days/12 months). p values and hazard ratios for time-to-event endpoints were calculated using the stratified log-rank test and stratified Cox regression, respectively. Stratification factors were induction treatment received and response to induction treatment. p values for response rates were calculated using the χ^2 test, and odds ratios were calculated using logistic regression (response rate analyses were unadjusted). [a] Clinical cut-off: January 14, 2009. Median observation time: 25.5 months. [b] Clinical cut-off: January 31, 2013. Median observation time: 73 months. [c] Based on investigator assessments.

MabThera maintenance treatment provided consistent benefit in all 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 or PR).

Maintenance therapy - relapsed/refractory follicular NHL

In a prospective, open label, international, multi-centre, phase III trial, 465 patients with relapsed/refractory follicular NHL 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 randomised to both parts of the study. After a median observation time of 31 months for patients randomised to the induction phase, R-CHOP significantly improved the outcome of patients with relapsed/refractory follicular NHL when compared to CHOP (see Table 7).

Table 7: Induction phase: overview of efficacy results for CHOP vs R-CHOP (31 months' median observation time)

	CHOP	R-CHOP	p-value	Risk Reduction[1)]
Primary Efficacy				
ORR[2)]	74%	87%	0.0003	na
CR[2)]	16%	29%	0.0005	na
PR[2)]	58%	58%	0.9449	na
Secondary Efficacy				
OS (median)	NR	NR	0.0508	32%
PFS (median)	19.4 mo.	33.2 mo.	0.0001	38%

[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 vs PR vs non-response ($p < 0.0001$). Abbreviations: NA, not available; NR, not reached; mo, months; ORR: overall response rate; CR: complete response; PR: partial response; OS: overall survival; PFS: progression free survival

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

The median time to new anti-lymphoma treatment was significantly longer with MabThera maintenance treatment than with observation (38.8 months vs. 20.1 months, $p < 0.0001$ log-rank test). The risk of starting a new treatment was reduced by 50% (95% CI; 30% - 64%). In patients achieving a CR/CRu (complete response unconfirmed) as best response during induction treatment, MabThera maintenance treatment significantly prolonged the median disease free survival (DFS) compared to the observation group (53.7 vs 16.5 months, $p=0.0003$), log-rank test (Table 8). The risk of relapse in complete responders was reduced by 67% (95% CI; 39% - 82%).

Table 8: Maintenance phase: overview of efficacy results MabThera vs. observation (28 months median observation time)

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

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

The benefit of MabThera maintenance treatment was confirmed in all subgroups analysed, regardless of induction regimen (CHOP or R-CHOP) or quality of response to induction treatment (CR or PR) (Table 8). MabThera maintenance treatment significantly prolonged median PFS in patients responding to CHOP induction therapy (median PFS 37.5 months vs 11.6 months, $p < 0.0001$) as well as in those responding to R-CHOP induction (median PFS 51.9 months vs 22.1 months, $p=0.0071$). MabThera maintenance treatment also provided a clinically meaningful benefit in terms of overall survival for both patients responding to CHOP and patients responding to R-CHOP in the induction phase of the study, although longer follow-up is required to confirm this observation.

MabThera maintenance treatment provided consistent benefit in all subgroups tested [gender (male, female), age (≤ 60 years, > 60 years), stage (III, IV), WHO performance status (0 vs > 0), B symptoms (absent, present), bone marrow involvement (no vs yes), IPI (0-2 vs 3-5), FLIPI score (0 - 1, vs 2 vs 3 - 5), number of extra-nodal sites (0 - 1 vs > 1), number of nodal sites (< 5 vs ≥ 5), number of previous regimens (1 vs 2), best response to prior therapy (CR/PR vs NC/PD), haemoglobin (< 12 g/dL vs ≥ 12 g/dL), β_2-microglobulin (< 3mg/L vs ≥ 3 mg/L), LDH (elevated, not elevated) except for the small subgroup of patients with bulky disease.

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 characteristics and disease status. The final analysis confirmed that R-CHOP significantly increased the duration of event-free survival (the primary efficacy parameter, where events were death, relapse or progression of lymphoma, or institution of a new anti-lymphoma treatment) (p=0.0001). Kaplan Meier estimates of the median duration of event-free survival were 35 months in the R-CHOP arm compared to 13 months in the CHOP arm, representing a risk reduction of 41%. At 24 months, estimates for overall survival were 68.2% in the R-CHOP arm compared to 57.4% in the CHOP arm. A subsequent analysis of the duration of overall survival, carried out with a median follow-up duration of 60 months, confirmed the benefit of R-CHOP over CHOP treatment (p=0.0071), representing a risk reduction of 32%.

The analysis of all secondary parameters (response rates, progression-free survival, disease-free survival, duration of response) verified the treatment effect of R-CHOP compared to CHOP. The complete response rate after cycle 8 was 76.2% in the R-CHOP group and 62.4% in the CHOP group (p = 0.0028). The risk of disease progression was reduced by 46% and the risk of relapse by 51%.

In all patient subgroups (gender, age, age adjusted IPI, Ann Arbor stage, ECOG, Beta 2 Microglobulin, LDH, Albumin, B-symptoms, Bulky disease, extranodal sites, bone marrow involvement), the risk ratios for event-free survival and overall survival (R-CHOP compared with CHOP) were less than 0.83 and 0.95 respectively. R-CHOP was associated with improvements in outcome for both high- and low-risk patients according to age adjusted IPI.

<u>Previously untreated and relapsed/refractory chronic lymphocytic leukaemia</u>
In two open-label randomised trials, a total of 817 previously untreated patients and 552 patients with relapsed/refractory CLL were randomised to receive either FC chemotherapy (fludarabine 25 mg/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 cycles 2-6. A total of 810 patients (403 R-FC, 407 FC) from the first line study (Table 9 and Table 10) and 552 patients (276 R-FC, 276 FC) for the relapsed/refractory study (Table 11) were analysed for efficacy.

In the first-line study, after a median observation time of 20.7 months, the median progression-free survival (PFS; primary endpoint) was a median of 40 months in the R-FC group and a median of 32 months in the FC group (p < 0.0001, log-rank test). The analysis of overall survival demonstrated improved survival in favour of the R-FC arm (p=0.0427, log-rank test). These results were confirmed with longer follow-up: 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) and overall survival analyses continued to show a significant benefit of R-FC treatment over FC chemotherapy alone (p = 0.0319, log-rank test). The benefit in terms of PFS was consistently observed in most patient subgroups analysed according to disease risk at baseline (i.e. Binet stages A-C) and was confirmed with longer follow-up (Table 10).

Table 9: First-line treatment of chronic lymphocytic leukaemia - overview of efficacy results for MabThera plus FC vs. FC alone (20.7 months' median observation time)

Efficacy Parameter	Kaplan-Meier Estimate of Median Time to Event (Months)			Hazard Ratio
	FC (n=407)	R-FC (n=403)	Log-Rank p value	
Progression-free survival	32.2 (32.8)***	39.8 (55.3)***	< 0.0001 (< 0.0001)***	0.56 (0.55)***
Overall Survival	NR (NR)***	NR (NR)***	0.0427 (0.0319)***	0.64 (0.73)***
Event Free Survival	31.1 31.3***	39.8 (51.8)***	< 0.0001 (< 0.0001)***	0.55 (0.56)***
Response rate (CR, nPR, or PR)	72.7%	86.1%	< 0.0001	n.a.
CR rates	17.2%	36.0%	< 0.0001	n.a.
Duration of response*	34.7 (36.2)***	40.2 (57.3)***	0.0040 (< 0.0001)***	0.61 (0.56)***
Disease free survival (DFS)**	NR (48.9)***	NR (60.3)***	0.7882 (0.0520)***	0.93 (0.69)***
Time to new CLL treatment	NR (47.2)***	NR (69.7)***	0.0052 (< 0.0001)***	0.65 (0.58)***

Response rate and CR rates analysed using Chi-squared Test. *: only applicable to patients with CR (complete response), nPR (nodular partial response) or PR (partial response) as end of treatment response. **: only applicable to patients with CR as end of treatment response ***: values in brackets correspond to 48.1 months median observation time (ITT population – 409 FC, 408 R-FC) NR: not reached; n.a. not applicable.

Table 10: Hazard ratios of progression-free survival according to Binet stage (ITT) – 20.7 months' median observation time

Progression-free survival (PFS)	Number of patients		Hazard Ratio (95% CI)	Log-Rank p value
	FC	R-FC		
Binet Stage A	22 (22)*	18 (18)*	0.13 (0.03; 0.61) (0.39 (0.15; 0.98))*	0.0025 (0.0370)*
Binet Stage B	257 (259)*	259 (263)*	0.45 (0.32; 0.63) (0.52 (0.41; 0.66))*	<0.0001 (<0.0001)*
Binet Stage C	126 (126)*	125 (126)*	0.88 (0.58; 1.33) (0.68 (0.49; 0.95))*	0.5341 (0.0215)*

CI: Confidence Interval. *: values correspond to 48.1 months median observation time (ITT population – 409 FC, 408 R-FC)

In the relapsed/refractory study, the median PFS (primary endpoint) was 30.6 months in the R-FC group and 20.6 months in the FC group (p=0.0002, log-rank test). The benefit in terms of PFS was observed in almost all patient subgroups analysed according to disease risk at baseline. A non-significant trend towards improvement in overall survival was reported in the R-FC arm compared to the FC arm.

Table 11: 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	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 with CR (complete response), nPR (nodular partial response), PR (partial response) as best overall response. **: only applicable to patients with CR as best overall response. NR: not reached; n.a. not applicable.

Results from other supportive studies using MabThera in combination with other chemotherapy regimens (including CHOP, FCM (fludarabine, cyclophosphamide, mitoxantrone), PC (pentostatin, cyclophosphamide), PCM (pentostatin, cyclophosphamide, mitoxantrone), bendamustine and cladribine) for the treatment of CLL patients have also demonstrated high overall response rates with promising PFS rates without adding relevant toxicity to the treatment.

Rheumatoid arthritis

The efficacy of MabThera in rheumatoid arthritis has been demonstrated in three pivotal, phase III, randomised, placebo-controlled, double-blind, multicentre studies. Eligible patients had severe active RA, 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. Each course was preceded by an IV infusion of 100 mg methylprednisolone. All patients received concomitant oral methotrexate. In addition, in Study WA17042, all patients received concomitant oral glucocorticoid on days 2-7 and on days 8-14 following the first infusion.

The retreatment criteria differed between the studies using one of two approaches; 'Treatment to Remission' whereby patients were treated no more frequently than every 6 months if not in DAS28 remission (i.e. DAS28-ESR $\geq$ 2.6) and 'Treatment as Needed' strategy ('Treatment PRN'), based on disease activity and/or return of clinical symptoms (swollen and tender joint counts $\geq$ 8) and treated no sooner than every 16 weeks.

Study WA17042 (REFLEX) included 517 patients that had experienced an inadequate response or intolerance to one or more TNF inhibitor therapies (TNF-IR). The primary endpoint was the proportion of patients who achieved an ACR20 response at week 24.

Patients received 2 x 1000 mg MabThera or placebo. Patients were followed beyond week 24 for long term endpoints, including radiographic assessment at 56 weeks. During this time patients could receive further courses of MabThera under an open label extension study protocol. In the open-label protocol patients received further courses based on the 'Treatment PRN' criteria.

Study WA17045 (SERENE) included 511 patients that had experienced an inadequate response to methotrexate (MTX-IR) and had not received prior biologic therapy. The primary endpoint was the proportion of patients who achieved an ACR20 response at week 24. Patients received either placebo, 2 x 500mg or 2 x 1000mg MabThera infusion. Patients were followed beyond week 24 for long term endpoints and could receive further courses of MabThera based on the 'Treatment to Remission' criteria. An active dose comparison was made at week 48.

Disease activity outcomes
In these studies, MabThera 2 x 1000 mg significantly increased the proportion of patients achieving at least a 20% improvement in ACR score compared with patients treated with methotrexate alone (Table 12). 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. Patients seropositive for disease related auto-antibodies (RF and/or anti CCP) demonstrated consistently high efficacy compared to MTX alone across studies. Efficacy in seropositive patients was higher than that observed in seronegative patients in whom efficacy was modest.

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 CRP (mg/dL).

Table 12: Cross-Study Comparison of ACR Responses (ITT Population)

	Timepoint	**ACR Response**	**Placebo+MTX**	**RTX+MTX** *(2 x 1000 mg)*
Study WA17042 (TNF-IR)	*Week 24*		*n=201*	*n=298*
		ACR20	36 (18%)	153 (51%)***
		ACR50	11 (5%)	80 (27%)***
		ACR70	3 (1%)	37 (12%)***
Study WA17045 (MTX-IR)	*Week 24*		*n=172*	*n=170*
		ACR20	40 (23%)	86 (51%)***
		ACR50	16 (9%)	44 (26%)***
		ACR70	9 (5%)	17 (10%)

Significant difference from placebo at the primary timepoint: * $p < 0.05$, **$p < 0.001$ ***$p \leq 0.0001$

Patients treated with MabThera had a significantly greater reduction in disease activity score (DAS28) than patients treated with methotrexate alone. A good to moderate EULAR response was achieved by significantly more MabThera treated patients compared to patients treated with methotrexate alone (Table 13).

Table 13: Cross-Study Comparison of DAS28-ESR and EULAR Responses (ITT Population)

	Placebo+MTX	**RTX +MTX** *(2 × 1000mg)*
Study WA17042 (TNF-IR)		
Change in DAS28 at Week 24		
n	*n=201*	*n=298*
Mean Change	-0.4	-1.9***
EULAR Response (Week 24)		
n	*n=201*	*n=298*
Moderate	20%	50%***
Good	2%	15%***
Study WA17045 (MTX-IR)		
Change in DAS28 at Week 24		
n	*n=171*	*n=168*
Mean Change	–0.8	–1.7***
EULAR response (Week 24)		
n	*n=172*	*n=170*
Moderate	29%	51%***
Good	5%	12%***

Significant difference from placebo at the primary timepoint: * $p < 0.05$, **$p < 0.001$ ***$p \leq 0.0001$

Inhibition of Joint Damage
In studies WA17042 and WA17047 structural joint damage was assessed radiographically and expressed as change in modified Total Sharp Score (TSS) and its components, the erosion score and joint space narrowing score.

In Study WA17042, conducted in TNF-IR patients receiving MabThera in combination with MTX demonstrated significantly less radiographic progression at 56 weeks than patients from the methotrexate alone group. A higher proportion of patients receiving MabThera also had no erosive progression over 56 weeks.

Study WA17047, conducted in MTX-naïve patients (755 patients with early rheumatoid arthritis of between 8 weeks to four years' duration), assessed the prevention of structural joint damage as its primary objective (see section 4.4). Patients received either placebo, 2 x 500 mg or 2 x 1000 mg MabThera infusion. From week 24 patients could receive further courses of MabThera (or placebo to week 104) based on the 'Treatment to Remission' criteria. The primary endpoint of change in modified Total Sharp Score (TSS) demonstrated that only treatment with MabThera at a dose of 2 x 1000 mg in combination with methotrexate significantly reduced the rate of progression of joint damage (PJD) at 52 weeks compared with placebo + MTX (Table 14). The reduction in PJD was driven mainly by a significant reduction in the change in Erosion Score.

Inhibition of the rate of progressive joint damage was also observed long term. Radiographic analysis at 2 years in study WA17042 demonstrated significantly reduced progression of structural joint damage in patients receiving MabThera (2 x 1000mg) + MTX compared to MTX alone as well as a significantly higher proportion of patients with no progression of joint damage over the 2-year period.

Table 14: Radiographic outcomes at 1 year in Studies WA17042 and WA17047 (MITT Population)

	Placebo+MTX	**RTX+MTX** *(2 ×1000 mg)*
Study WA17042 (TNF-IR)	*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
Study WA17047 (MTX-naïve)	*n=232*	*n=244*
Mean Change from Baseline:		
Modified Total Sharp Score	1.079	0.359**
Erosion Score	0.738	0.233***
Joint Space Narrowing Score	0.341	0.126
Proportion of patients with no radiographic change	53%	64%*
Proportion of patients with no erosive change	55%	67%*

Radiographic outcomes were assessed at Week 52 in Study WA17047 and Week 56 in Study WA17042. 150 patients originally randomised to placebo + MTX in WA17042 received at least one course of RTX + MTX by one year * p <0 05, ** p < 0.001, *** p < 0.0001, NS not significant

Quality of life outcomes

MabThera treated patients reported an improvement in all patient-reported outcomes (HAQ-DI, FACIT-Fatigue and SF-36 questionnaires). Significant reductions in disability index (HAQ-DI), fatigue (FACIT-Fatigue), and improvement in the physical domains of the SF-36 were observed in patients treated with MabThera compared to patients treated with methotrexate alone.

Table 15: Cross Study Comparison of HAQ-DI and FACIT-Fatigue responses

	Placebo+MTX[1]	**RTX+MTX[1]** ***(2 × 1000mg)***
Study WA17042 (TNF-IR)	*n=201*	*n=298*
- *Mean change in HAQ[a] at Week 24*	-0.1	-0.4***
- *% patients with HAQ MCID at Week 24*	20%	51%
- *Mean change in FACIT-Fatigue[b] at Week 24*	-0.5	-9.1***
Study WA17045 (MTX-IR)	*n=172[a] (170)[b]*	*n=170[a] (168)[b]*
- *Mean change in HAQ[a] at Week 24*	-0.21	-0.42***

	Placebo+MTX[1]	RTX+MTX[1] *(2 × 1000mg)*
- *% patients with HAQ MCID at Week 24*	48%	58%*
- *Mean change in FACIT-Fatigue[b] at Week 24*	2.7	6.4***

[a] Health assessment questionnaire (HAQ),[b] Functional assessment of chronic illness therapy (FACIT-Fatigue). Significant difference from placebo at the primary timepoint: * p < 0.05, **p < 0.001 ***p ≤ 0.0001. (CMH test for categorical change, ANOVA for mean change, note that the unadjusted mean changes are displayed)

Table 16: Cross Study Comparison of Short Form Health Survey (SF-36)

	Placebo+MTX	RTX +MTX *(2 × 1000 mg)*
Study WA17042 (TNF-IR)	*n=197*	*n=294*
Physical Health		
Mean change at Week 24	0.9	5.8***
% patients with MCID at Week 24	13%	48%***
Mental Health		
Mean change at Week 24	1.3	4.7**
% patients with MCID at Week 24	20%	38%**
Study WA17045 (MTX-IR)	*n=147*	*n=155*
Physical Health		
Mean change at Week 24	2.7	5.9***
% patients with MCID at Week 24	31%	48%
Mental Health		
Mean change at Week 24	2.1	4.4**
% patients with MCID at Week 24	24%	35%*

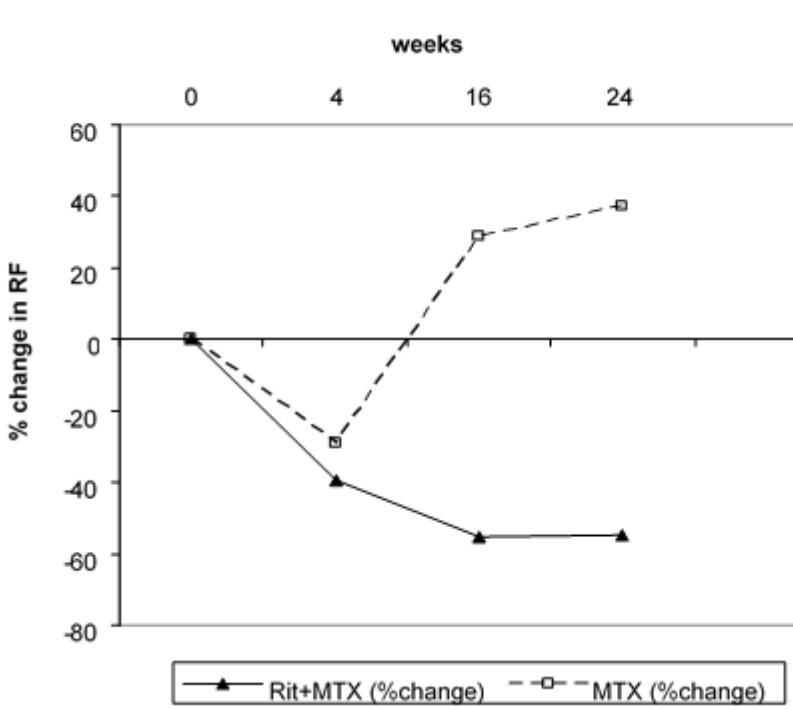
MCID = minimum clinically important difference defined as an increase of: >6.33 for mental health score and > 5.42 for physical health score, % of patients based on number of patients assessable (n) Significant difference from placebo at the primary timepoint: * p < 0.05, ** p < 0.001, *** p < 0.0001 (CMH test for categorical change, ANOVA for mean change - note that unadjusted mean changes are displayed)

Laboratory evaluations

Approximately 10% of patients with RA tested positive for HACA in clinical studies. 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, and failure to deplete B cells after receipt of further treatment courses has been observed rarely.

In rheumatoid factor (RF) positive patients, marked decreases were observed in rheumatoid factor concentrations following treatment with rituximab in all three studies (range 45-64%, Figure 1).

Figure 1: Percentage Change in Total RF Concentration Over Time in Study 1 (ITT Population, RF-Positive Patients)



Plasma total immunoglobulin concentrations, total lymphocyte counts, and white cells generally remained within normal limits following MabThera treatment, with the exception of a transient drop in white cell counts over the first four weeks following therapy. Titres of IgG antigen specific antibody to mumps, rubella, varicella, tetanus toxoid, influenza and streptococcus pneumococci remained stable over 24 weeks following exposure to MabThera in rheumatoid arthritis patients.

Effects of rituximab on a variety of biomarkers were evaluated in patients enrolled into a clinical study. This sub study evaluated the impact of a single treatment course of rituximab on levels of biochemical markers, including markers of inflammation [Interleukin 6, C Reactive protein, Serum amyloid type A protein, Protein S100 isotypes A8 and A9], autoantibody (RF and anti-cyclic citrullinated peptide immunoglobulin) production and bone turnover [osteocalcin and procollagen 1 N terminal peptide (P1NP)]. Rituximab treatment, whether as monotherapy or in combination with methotrexate or cyclophosphamide reduced the levels of inflammatory markers significantly, relative to methotrexate alone, over the first 24 weeks of follow-up. Levels of markers of bone turnover, osteocalcin and P1NP, increased significantly in the rituximab groups compared to methotrexate alone.

Long-term efficacy with multiple course therapy

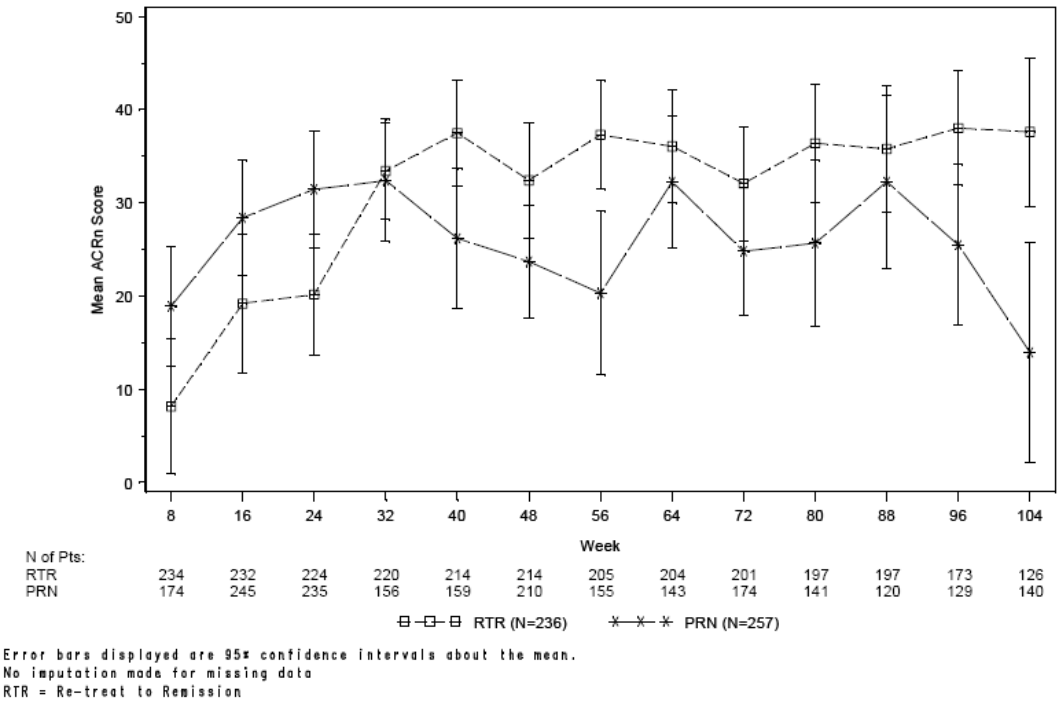
In clinical studies patients were retreated based on either a ‘Treatment to Remission’ or a ‘Treatment PRN’ strategy. Repeat courses of MabThera maintained or improved treatment benefit, irrespective of the treatment strategy (Treatment to Remission or Treatment PRN) (Figure 2). However, Treatment to Remission generally provided better responses and tighter control of disease activity as indicated by ACRn, DAS28-ESR and HAQ-DI scores over time. Patients treated PRN also experienced returning disease symptoms between courses, as evidenced by DAS28-ESR scores which were close to pre-treatment levels prior to each course (Table 17).

Table 17: Baseline Values Prior to Each Course for Parameters of Disease Activity

Population	Parameter	C1	C2	C3	C4	C5
Treatment To Remission		*n=236*	*n=218*	*n=198*	*n=156*	*n=83*
	Mean BL DAS	6.6	4.9	4.6	4.6	4.7
	Median BL ACRn	-	22.7	25.5	26.5	26.3
Treatment PRN		*n=257*	*n=182*	*n=139*	*n=85*	*n=39*
	Mean BL DAS	6.7	6.2	6.2	5.9	6.0
	Median BL ACRn	-	-5.3	-11.1	-10.9	-4.2

Positive change in ACRn = improvement; BL=baseline

Figure 2: Plot of Mean ACRn Over Time by Treatment Criteria (MTX-IR Population



120-minute infusion rate study (ML25641)
In a multi-centre, open-label single-arm trial, 351 patients with moderate-to-severe active RA, who had an inadequate response to at least one TNF inhibitor and were receiving MTX, were to receive 2 courses of MabThera treatment. Patients who were naïve to prior MabThera therapy (n=306) and those who had received 1 to 2 prior courses of MabThera 6-9 months prior to baseline (n=45), were eligible for enrolment.

Patients received 2 courses of MabThera 2 x 1000mg + MTX treatment with the first course administered on Days 1 and 15 and the second course six-months later on Days 168 and 182. The first infusion of the first course (Day 1 infusion) was administered over a 4.25-hour

period. The second infusion of the first course (Day 15 infusion) and both infusions in the second course (Day 168 and 182 infusions) were administered over 120 minutes. Any patient experiencing a serious infusion-related reaction (IRR) with any infusion was withdrawn from the study.

The primary objective of this study was to assess the safety of administering the second infusion of the first study course of MabThera over 120 minutes.

The incidence of IRRs at Day 15 was 6.5% (95% CI [4.1%-9.7%]) consistent with the rate observed historically. There were no serious IRRs observed. Data observed for the infusions on Days 168 and 182 (120-minute infusion) demonstrates a low incidence of IRRs, similar to the rate observed historically, with no serious IRRs occurring (see section 4.8).

Granulomatosis with polyangiitis (Wegener's) and Microscopic polyangiitis
A total of 197 patients with severely active GPA and MPA were enrolled and treated in an active controlled, randomised, double-blind, multicenter, non-inferiority study. Patients were 15 years of age or older, diagnosed with severely active GPA (75% of patients) or MPA (24% of patients) according to the Chapel Hill Consensus conference criteria (1% of patients had unknown GPA and MPA type).

Patients were randomised in a 1:1 ratio to receive either oral cyclophosphamide (CYC) daily (2mg/kg/day) for 3-6 months followed by azathioprine, or MabThera (375 mg/m^2) once weekly for 4 weeks. Patients in both arms received 1000 mg of pulse 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 (CR) 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 CYC for CR at 6 months (Table 18). In addition, the CR rate in the MabThera arm was significantly greater than the estimated CR rate in patients with severe GPA and MPA not treated or treated only with glucocorticoids, based on historical control data.

Efficacy was observed both for patients with newly diagnosed GPA and MPA and for patients with relapsing disease.

Table 18: Percentage of Patients who achieved Complete Remission at 6 Months (Intent- to-Treat Population)

	MabThera (n=99)	**CYC** (n=98)	**Treatment Difference** (MabThera-CYC)
Rate	63.6%	53.1%	10.6%
95.1%[b] CI	(54.1%, 73.2%)	(43.1%, 63.0%)	(-3.2%, 24.3)[a]

CI = confidence interval.[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.

5.2 PHARMACOKINETIC PROPERTIES

Distribution and elimination

Non-Hodgkin's lymphoma

Based on a population pharmacokinetic analysis in 298 NHL patients who received single or multiple infusions of rituximab as a single agent or in combination with CHOP therapy, the typical population estimates of nonspecific clearance (CL_1), specific clearance (CL_2) likely contributed by B cells or tumour burden, and central compartment volume of distribution (V_1) were 0.14 L/day, 0.59 L/day, and 2.7 L, respectively. The estimated median terminal elimination half-life of rituximab was 22 days (range 6.1 to 52 days). Baseline CD19-positive cell counts and size of measurable tumour lesions contributed to some of the variability in CL_2 of rituximab in data from 161 patients given 375 mg/m^2 as an IV infusion for 4 weekly doses. Patients with higher CD19-positive cell counts or tumour lesions had a higher CL_2. However, a large component of inter-individual variability remained for CL_2 after correction for CD19-positive cell counts and tumour lesion size. V_1 varied by body surface area (BSA) and CHOP therapy. This variability in V_1 (27.1% and 19.0%) contributed by the range in BSA (1.53 to 2.32 m^2) and concurrent CHOP therapy, respectively, were relatively small. Age, gender, race, and WHO performance status had no effect on the pharmacokinetics of rituximab. This analysis suggests that dose adjustment of rituximab with any of the tested covariates is not expected to result in a meaningful reduction in its pharmacokinetic variability.

Rituximab at a dose of 375 mg/m^2 was administered as an IV infusion at weekly intervals for 4 doses to 203 patients with NHL naive to rituximab. The mean C_{max} following the fourth infusion was 486 mcg/mL (range 77.5 to 996.6 mcg/mL). The peak and trough serum levels of rituximab were inversely correlated with baseline values for the number of circulating CD19-positive B-cells and measures of disease burden. Median steady-state serum levels were higher for responders compared with non-responders. Serum levels were higher in patients with International Working Formulation (IWF) subtypes B, C, and D as compared with those with subtype A. Rituximab was detectable in the serum of patients 3 - 6 months after completion of last treatment.

Rituximab at a dose of 375 mg/m^2 was administered as an IV infusion at weekly intervals for 8 doses to 37 patients with NHL. The mean C_{max} increased with each successive infusion, spanning from a mean of 243 mcg/mL (range 16 – 582 mcg/mL) after the first infusion to 550 mcg/mL (range 171 – 1177 mcg/mL) after the eighth infusion.

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

Chronic lymphocytic leukaemia

Rituximab was administered as an 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 mcg/mL (range, 97 – 764 mcg/mL) after the fifth 500 mg/m^2 infusion.

Rheumatoid arthritis

Following two intravenous infusions of rituximab 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.

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 mcg/mL for 2 x 500 mg dose and ranged from 298 to 341 mcg/mL for 2 x 1000 mg dose. Following second infusion, mean C_{max} ranged from 183 to 198 mcg/mL for the 2 × 500 mg dose and ranged from 355 to 404 mcg/mL for the 2 × 1000 mg dose. Mean terminal elimination half-life ranged from 15 to 16.5 days for the 2 x 500 mg dose group and 17 to 21 days for the 2 × 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 mcg/mL for 2 x 500 mg dose and 317 to 370 mcg/mL for 2 x 1000 mg dose. C_{max} following second infusion, was 207 mcg/mL for the 2 x 500 mg dose and ranged from 377 to 386 mcg/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 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 mcg/mL and a mean terminal half-life of 19.2 days.

Granulomatosis with polyangiitis (Wegener's) (GPA) and Microscopic polyangiitis (MPA)
Based on the population pharmacokinetic analysis of data in 97 GPA and MPA patients who received 375 mg/m^2 rituximab once weekly for four doses, the estimated median terminal elimination half-life was 23 days (range 9 to 49 days). Rituximab mean clearance and volume of distribution were 0.313 L/day (range 0.116 to 0.726 L/day) and 4.50 L (range 2.25 to 7.39 L), respectively. The PK parameters of rituximab in GPA and MPA patients appear similar to what has been observed in RA patients (see section 5.2).

Pharmacokinetics in special populations
No pharmacokinetic data are available in patients with hepatic or renal impairment.

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

Developmental toxicity studies have been performed in cynomolgus monkeys at doses up to 100 mg/kg (treatment on gestation days 20-50) and have revealed no evidence of toxicity to the foetus due to rituximab. However, dose-dependent pharmacologic depletion of B cells in the lymphoid organs of the foetuses was observed, which persisted post 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 immunisation.

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium citrate dihydrate
Polysorbate 80
Sodium chloride
Water for injection
Hydrochloric acid or sodium hydroxide (pH adjusted to 6.5).

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

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

Storage after dilution

After aseptic dilution with 0.9% aqueous saline solution
The prepared infusion solution of MabThera is physically and chemically stable for 30 days at 2 °C – 8 °C while protected from light, plus an additional 24 hours at room temperature (≤30°C) in diffuse light.

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

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

6.4 SPECIAL PRECAUTIONS FOR STORAGE

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

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

6.5 NATURE AND CONTENTS OF CONTAINER

Clear Type I glass vials with butyl rubber stopper.

MabThera 100 mg in 10 mL vials (rituximab 10 mg/mL) pack of 2 vials

MabThera 500 mg in 50 mL vials (rituximab 10 mg/mL) pack of 1 vial.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Disposal

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

Instructions for dilution

Withdraw the required amount of MabThera under aseptic conditions and dilute to a calculated rituximab concentration of 1 – 4 mg/mL in an infusion bag containing sterile, non-pyrogenic 0.9% aqueous saline solution or 5% aqueous dextrose solution. To mix the solution, gently invert the bag to avoid foaming. Care must be taken to ensure the sterility of prepared solutions. Since MabThera does not contain any anti-microbial preservative or bacteriostatic agents, aspetic technique must be observed. Parenteral medications should be inspected visually for particulate matter or discoloration prior to administration.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Roche Products (New Zealand) Limited
PO Box 109113 Newmarket
Auckland 1149
NEW ZEALAND

Medical enquiries: 0800 276 243

9. DATE OF FIRST APPROVAL

11 March 1999

10. DATE OF REVISION OF THE TEXT

16 May 2019

Summary of Changes Table

Section Changed	Summary of new information
4.4	Update to Special Warnings and Precautions for Use wording related to patient's immunisation status. The immunisation recommendation is applicable to all patients in all approved autoimmune indications, not only RA patients.