SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

MabThera 100 mg concentrate for solution for infusion

Each mL contains 10 mg ofrituximab.
Each 10 mL vial contains 100 mg ofrituximab.

MabThera 500 mg concentrate for solution for infusion

Each mL contains 10 mg ofrituximab.
Each 50 mL vial contains 500 mg ofrituximab.

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

Excipients with known effects

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

For the full list ofexcipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear, colourless liquid with pH of6.2 – 6.8 and osmolality of324 - 396 mOsmol/kg .

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

MabThera is indicated in adults for the following indications:

Non-Hodgkin's lymphoma (NHL)

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

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

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

MabThera is indicated for the treatment ofadult patients with CD20 positive di**f** use large B cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy.
MabThera in combination with chemotherapy is indicated for the treatment ofpaediatric patients (aged ≥ 6 months to < 18 years old) with previously untreated advanced stage CD20 positive di**f** use large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL)/Burkitt leukaemia (mature B-cell acute leukaemia) (BAL) or Burkitt-like lymphoma (BLL).

Chronic lymphocytic leukaemia (CLL)

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

See section 5.1 for further information.

Rheumatoid arthritis

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

MabThera has been shown to reduce the rate ofprogression ofjoint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate.

Granulomatosis with polyangiitis and microscopic polyangiitis

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

MabThera, in combination with glucocorticoids, is indicated for the induction ofremission in paediatric patients (aged ≥ 2 to < 18 years old) with severe, active GPA (Wegener's) and MPA.

Pemphigus vulgaris

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

4.2 Posology and method ofadministration

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

Premedication and prophylactic medications

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

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

In paediatric patients with non Hodgkin's lymphoma, premedication with paracetamol and H1 antihistamine (= diphenhydramine or equivalent) should be administered 30 to 60 minutes before the start ofthe infusion ofMabThera. In addition, prednisone should be given as indicated in Table 1.

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

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

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

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

Paediatric population
In paediatric patients with GPA or MPA, prior to the first MabThera IV infusion, methylprednisolone should be given IV for three daily doses of 30 mg/kg/day (not to exceed 1 g/day) to treat severe vasculitis symptoms. Up to three additional daily doses of 30 mg/kg IV methylprednisolone can be given prior to the first MabThera infusion.

Following completion of IV methylprednisolone administration, patients should receive oral prednisone 1 mg/kg/day (not to exceed 60 mg/day) and tapered as rapidly as possible per clinical need (see section 5.1).

Pneumocystis jirovecii pneumonia (PJP) prophylaxis is recommended for paediatric patients with GPA or MPA during and following MabThera treatment, as appropriate.

Posology

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

Non-Hodgkin's lymphoma

Follicular non-Hodgkin's lymphoma

Combination therapy
The recommended dose of MabThera in combination with chemotherapy for induction treatment of previously untreated or relapsed/refractory patients with follicular lymphoma is: 375 mg/m^2 body surface area per cycle, for up to 8 cycles.

MabThera should be administered on day 1 ofeach chemotherapy cycle, after intravenous administration ofthe glucocorticoid component ofthe chemotherapy ifapplicable.

Maintenance therapy

- Previously untreated follicular lymphoma

The recommended dose of MabThera used as a maintenance treatment for patients with previously untreated follicular lymphoma who have responded to induction treatment is: 375 mg/m^2 body surface area once every 2 months (starting 2 months after the last dose ofinduction therapy) until disease progression or for a maximum period oftwo years (12 infusions in total).

- Relapsed/refractory follicular lymphoma

The recommended dose of MabThera used as a maintenance treatment for patients with relapsed/refractory follicular lymphoma who have responded to induction treatment is: 375 mg/m^2 body surface area once every 3 months (starting 3 months after the last dose ofinduction therapy) until disease progression or for a maximum period oftwo years (8 infusions in total).

Monotherapy

- Relapsed/refractory follicular lymphoma

The recommended dose of MabThera monotherapy used as induction treatment for adult patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy is: 375 mg/m^2 body surface area, administered as an intravenous infusion once weekly for four weeks.

For retreatment with MabThera monotherapy for patients who have responded to previous treatment with MabThera monotherapy for relapsed/refractory follicular lymphoma, the recommended dose is: 375 mg/m^2 body surface area, administered as an intravenous infusion once weekly for four weeks (see section 5.1).

Adult Diffuse large B cell non-Hodgkin's lymphoma

MabThera should be used in combination with CHOP chemotherapy. The recommended dosage is 375 mg/m^2 body surface area, administered on day 1 ofeach chemotherapy cycle for 8 cycles after intravenous infusion ofthe glucocorticoid component of CHOP. Safety and efficacy of MabThera have not been established in combination with other chemotherapies in diffuse large B cell non-Hodgkin's lymphoma.

Dose adjustments during treatment

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

Chronic lymphocytic leukaemia

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

Rheumatoid arthritis

Patients treated with MabThera must be given the patient alert card with each infusion.

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

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

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

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

Patients treated with MabThera must be given the patient alert card with each infusion.

Adult induction of remission
The recommended dosage of MabThera for induction of remission therapy in adult patients with GPA and MPA is 375 mg/m^2 body surface area, administered as an intravenous infusion once weekly for 4 weeks (four infusions in total).

Adult maintenance treatment
Following induction of remission with MabThera, maintenance treatment in adult patients with GPA and MPA should be initiated no sooner than 16 weeks after the last MabThera infusion.

Following induction of remission with other standard of care immunosuppressants, MabThera maintenance treatment should be initiated during the 4 week period that follows disease remission.

MabThera should be administered as two 500 mg IV infusions separated by two weeks, followed by a 500 mg IV infusion every 6 months thereafter. Patients should receive MabThera for at least 24 months after achievement of remission (absence of clinical signs and symptoms). For patients who may be at higher risk for relapse, physicians should consider a longer duration of MabThera maintenance therapy, up to 5 years.

Pemphigus vulgaris

Patients treated with MabThera must be given the patient alert card with each infusion.

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

Maintenance treatment
A maintenance infusion of 500 mg IV should be administered at months 12 and 18, and then every 6 months thereafter if needed, based on clinical evaluation.

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

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

Special populations

Paediatric population

Non-Hodgkin's lymphoma

In paediatric patients from ≥ 6 months to < 18 years of age with previously untreated, advanced stage CD20 positive DLBCL/BL/BAL/BLL, MabThera should be used in combination with systemic Lymphome Malin B (LMB) chemotherapy (see Tables 1 and 2). The recommended dosage of MabThera is 375mg/m2 BSA, administered as an IV infusion. No MabThera dose adjustments, other than by BSA, are required.

The safety and efficacy of MabThera paediatric patients ≥ 6 months to < 18 years of age has not been established in indications other than previously untreated advanced stage CD20 positive DLBCL/BL/BAL/BLL. Only limited data are available for patients under 3 years of age. See section 5.1 for further information.

MabThera should not be used in paediatric patients from birth to < 6 months ofage with CD20 positive diffuse large B-cell lymphoma (see section 5.1)

Table 1 Posology of MabThera administration for Non-Hodgkin's lymphoma paediatric patients

Cycle	Day oftreatment	Administration details
Prephase (COP)	No MabThera given	-
Induction course 1 (COPDAM1)	Day -2 (corresponding to day 6 ofthe prephase) 1st MabThera infusion	During the 1st induction course, prednisone is given as part ofthe chemotherapy course, and should be administered prior to MabThera.
	Day 1 2nd MabThera infusion	MabThera will be given 48 hours after thefirst infusion of MabThera.
Induction course 2 (COPDAM2)	Day -2 3rd MabThera infusion	In the 2nd induction course, prednisone is not given at the time ofMabThera administration.
	Day 1 4th MabThera infusion	MabThera will be given 48 hours after the third infusion of MabThera.
Consolidation course 1 (CYM/CYVE)	Day 1 5th MabThera infusion	Prednisone is not given at the time ofMabThera administration.
Consolidation course 2 (CYM/CYVE)	Day 1 6th MabThera infusion	Prednisone is not given at the time ofMabThera administration.
Maintenance course 1 (M1)	Day 25 to 28 of consolidation course 2 (CYVE) No MabThera given	Starts when peripheral counts have recovered from consolidation course 2 (CYVE) with ANC> 1.0 x 10^9/l and platelets > 100 x 10^9/l
Maintenance course 2 (M2)	Day 28 ofmaintenance course 1 (M1) No MabThera given	-

ANC = Absolute Neutrophil Count; COP = Cyclophosphamide, Vincristine, Prednisone; COPDAM = Cyclophosphamide, Vincristine, Prednisolone, Doxorubicin, Methotrexate; CYM = CYtarabine (Aracytine, Ara-C), Methotrexate; CYVE = CYtarabine (Aracytine, Ara-C), VEposide (VP16)

Table 2 Treatment Plan for Non-Hodgkin's lymphoma paediatric patients: Concomitant Chemotherapy with MabThera

Treatment Plan	Patient Staging	Administration details
Group B	Stage III with high LDH level (> N x 2), Stage IV CNS negative	Prephase followed by 4 courses: 2 induction courses (COPADM) with HDMTX 3g/m^2 and 2 consolidation courses (CYM)
Group C	Group C1: B- AL CNS negative, Stage IV & BAL CNS positive and CSF negative	Prephase followed by 6 courses: 2 induction courses (COPADM) with HDMTX 8g/m^2, 2 consolidation courses (CYVE) and 2 maintenance courses (M1 and M2)
	Group C3: BAL CSF positive, Stage IV CSF positive	
Consecutive courses should be given as soon as blood count recovery and patient's condition allows except for the maintenance courses which are given at 28 day intervals		
BAL = Burkitt leukaemia (mature B-cell acute leukaemia); CSF = Cerebrospinal Fluid; CNS = Central Nervous System; HDMTX = High-dose Methotrexate; LDH = Lactic Acid Dehydrogenase		

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

Induction of remission

The recommended dosage of MabThera for induction of remission therapy in paediatric patients with severe, active GPA or MPA is 375 mg/m^2 BSA, administered as an IV infusion once weekly for 4 weeks.

The safety and efficacy of MabThera in paediatric patients (≥ 2 to < 18 years of age) has not been established in indications other than severe, active GPA or MPA.
MabThera should not be used in paediatric patients less than 2 years of age with severe, active GPA or MPA as there is a possibility of an inadequate immune response towards childhood vaccinations against common, vaccine preventable childhood diseases (e.g. measles, mumps, rubella, and poliomyelitis) (see section 5.1).

Elderly

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

Method of administration

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

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

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

First infusion

The recommended initial rate for infusion is 50 mg/h; after the first 30 minutes, it can be escalated in 50 mg/h increments every 30 minutes, to a maximum of400 mg/h.

Subsequent infusions

All indications

Subsequent doses of MabThera can be infused at an initial rate of 100 mg/h, and increased by 100 mg/h increments at 30 minute intervals, to a maximum of400 mg/h.

Paediatric patients – non-Hodgkin's lymphoma

First infusion

The recommended initial rate for infusion is 0.5 mg/kg/h (maximum 50 mg/h); it can be escalated by 0.5 mg/kg/h every 30 minutes ifthere is no hypersensitivity or infusion-related reactions, to a maximum of400 mg/h.

Subsequent infusions

Subsequent doses of MabThera can be infused at an initial rate of 1 mg/kg/h (maximum 50 mg/h); it can be increased by 1 mg/kg/h every 30 minutes to a maximum of 400 mg/h.

Rheumatoidarthritis only

Alternative subsequent, faster, infusion schedule

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

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

4.3 Contraindications

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

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

Active, severe infections (see section 4.4).

Patients in a severely immunocompromised state.

Contraindications for use in rheumatoid arthritis, granulomatosis with polyangiitis, microscopic polyangiitis and pemphigus vulgaris

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

Active, severe infections (see section 4.4).

Patients in a severely immunocompromised state.

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

4.4 Special warnings and precautions for use

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

Progressive multifocal leukoencephalopathy

All patients treated with MabThera for rheumatoid arthritis, GPA, MPA or pemphigus vulgaris must be given the patient alert card with each infusion. The alert card contains important safety information for patients regarding potential increased risk ofinfections, including progressive multifocal leukoencephalopathy (PML).

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

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

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

Ifa patient develops PML, the dosing of MabThera must be permanently discontinued.

Following reconstitution ofthe immune system in immunocompromised patients with PML, stabilisation or improved outcome has been seen. It remains unknown ifearly detection ofPML and suspension of MabThera therapy may lead to similar stabilisation or improved outcome.

Non-Hodgkin's lymphoma and chronic lymphocytic leukaemia

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

This set ofreactions which includes syndrome ofcytokine release, tumour lysis syndrome and anaphylactic and hypersensitivity reactions are described below. They are not specifically related to the route ofadministration ofMabThera and can be observed with both formulations.

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

Severe cytokine release syndrome is characterised by severe dyspnoea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. This syndrome may be associated with some features oftumour lysis syndrome such as hyperuricaemia, hyperkalaemia, hypocalcaemia, hyperphosphataemia, acute renal failure, elevated lactate dehydrogenase (LDH) and may be associated with acute respiratory failure and death. The acute respiratory failure may be accompanied by events such as pulmonary interstitial infiltration or oedema, visible on a chest X-ray. The syndrome frequently manifests itselfwithin one or two hours ofinitiating the first infusion. Patients with a history ofpulmonary insufficiency or those with pulmonary tumour infiltration may be at greater risk ofpoor outcome and should be treated with increased caution. Patients who develop severe cytokine release syndrome should have their infusion interrupted immediately (see section 4.2) and should receive aggressive symptomatic treatment. Since initial improvement ofclinical symptoms may be followed by deterioration, these patients should be closely monitored until tumour lysis syndrome and pulmonary infiltration have been resolved or ruled out. Further treatment ofpatients after complete resolution ofsigns and symptoms has rarely resulted in repeated severe cytokine release syndrome.

Patients with a high tumour burden or with a high number ($\geq$25 x 10^9/L) ofcirculating malignant cells such as patients with CLL, who may be at higher risk ofespecially severe cytokine release syndrome, should be treated with extreme caution. These patients should be very closely monitored throughout the first infusion. Consideration should be given to the use ofa 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 ifthe lymphocyte count is still >25 x 10^9/L.

Infusion-related adverse reactions ofall kinds have been observed in 77% ofpatients treated with MabThera (including cytokine release syndrome accompanied by hypotension and bronchospasm in 10% ofpatients) see section 4.8. These symptoms are usually reversible with interruption of MabThera infusion and administration ofan anti-pyretic, an antihistaminic and occasionally oxygen, intravenous saline or bronchodilators, and glucocorticoids ifrequired. Please see cytokine release syndrome above for severe reactions.

Anaphylactic and other hypersensitivity reactions have been reported following the intravenous administration ofproteins to patients. In contrast to cytokine release syndrome, true hypersensitivity reactions typically occur within minutes after starting infusion. Medicinal products for the treatment of hypersensitivity reactions, e.g. epinephrine (adrenaline), antihistamines and glucocorticoids, should be available for immediate use in the event ofan allergic reaction during administration ofMabThera. Clinical manifestations ofanaphylaxis may appear similar to clinical manifestations ofthe cytokine release syndrome (described above). Reactions attributed to hypersensitivity have been reported less frequently than those attributed to cytokine release.

Additional reactions reported in some cases were myocardial infarction, atrial fibrillation, pulmonary oedema and acute reversible thrombocytopenia.

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

Cardiac disorders

Angina pectoris, cardiac arrhythmias such as atrial flutter and fibrillation, heart failure and/or myocardial infarction have occurred in patients treated with MabThera. Therefore patients with a history ofcardiac disease and/or cardiotoxic chemotherapy should be monitored closely.

Haematological toxicities

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

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

Infections
Serious infections, including fatalities, can occur during therapy with MabThera (see section 4.8). MabThera should not be administered to patients with an active, severe infection (e.g. tuberculosis, sepsis and opportunistic infections, see section 4.3).

Physicians should exercise caution when considering the use of MabThera in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection (see section 4.8).

Cases ofhepatitis B reactivation have been reported in subjects receiving MabThera including fulminant hepatitis with fatal outcome. The majority ofthese subjects were also exposed to cytotoxic chemotherapy. Limited information from one study in relapsed/refractory CLL patients suggests that MabThera treatment may also worsen the outcome ofprimary hepatitis B infections. Hepatitis B virus (HBV) screening should be performed in all patients before initiation oftreatment with MabThera. At minimum this should include HBsAg-status and HBcAb-status. These can be complemented with other appropriate markers as per local guidelines. Patients with active hepatitis B disease should not be treated with MabThera. Patients with positive hepatitis B serology (either HBsAg or HBcAb) should consult liver disease experts before start oftreatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation.

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

Immunisations
The safety ofimmunisation with live viral vaccines, following MabThera therapy has not been studied for NHL and CLL patients and vaccination with live virus vaccines is not recommended. Patients treated with MabThera may receive non-live vaccinations; however, with non-live vaccines response rates may be reduced. In a non-randomised study, adult patients with relapsed low-grade NHL who received MabThera monotherapy when compared to healthy untreated controls had a lower rate of response to vaccination with tetanus recall antigen (16% vs. 81%) and Keyhole Limpet Haemocyanin (KLH) neoantigen (4% vs. 76% when assessed for >2-fold increase in antibody titer). For CLL patients, similar results are assumable considering similarities between both diseases but that has not been investigated in clinical trials.

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

Skin reactions
Severe skin reactions such as Toxic Epidermal Necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome, some with fatal outcome, have been reported (see section 4.8). In case of such an event, with a suspected relationship to MabThera, treatment should be permanently discontinued.

Paediatric population
Only limited data are available for patients under 3 years ofage. See section 5.1 for further information.

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

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

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

Severe IRRs with fatal outcome have been reported in rheumatoid arthritis patients in the post-marketing setting. In rheumatoid arthritis most infusion-related events reported in clinical trials were mild to moderate in severity. The most common symptoms were allergic reactions like headache, pruritus, throat irritation, flushing, rash, urticaria, hypertension, and pyrexia. In general, the proportion ofpatients experiencing any infusion reaction was higher following the first infusion than following the second infusion ofany treatment course. The incidence of IRR decreased with subsequent courses (see section 4.8). The reactions reported were usually reversible with a reduction in rate, or interruption, of MabThera infusion and administration ofan anti-pyretic, an antihistamine, and, occasionally, oxygen, intravenous saline or bronchodilators, and glucocorticoids ifrequired. Closely monitor patients with pre-existing cardiac conditions and those who experienced prior cardiopulmonary adverse reactions. Depending on the severity ofthe IRR and the required interventions, temporarily or permanently discontinue MabThera. In most cases, the infusion can be resumed at a 50% reduction in rate (e.g. from 100 mg/h to 50 mg/h) when symptoms have completely resolved.

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

There are no data on the safety of MabThera in patients with moderate heart failure (NYHA class III) or severe, uncontrolled cardiovascular disease. In patients treated with MabThera, the occurrence of pre-existing ischemic cardiac conditions becoming symptomatic, such as angina pectoris, has been observed, as well as atrial fibrillation and flutter. Therefore, in patients with a known cardiac history, and those who experienced prior cardiopulmonary adverse reactions, the risk ofcardiovascular complications resulting from infusion reactions should be considered before treatment with MabThera and patients closely monitored during administration. Since hypotension may occur during MabThera infusion, consideration should be given to withholding anti-hypertensive medications 12 hours prior to the MabThera infusion.

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

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

Infections
Based on the mechanism ofaction of MabThera and the knowledge that B cells play an important role in maintaining normal immune response, patients have an increased risk ofinfection following MabThera therapy (see section 5.1). Serious infections, including fatalities, can occur during therapy with MabThera (see section 4.8). MabThera should not be administered to patients with an active, severe infection (e.g. tuberculosis, sepsis and opportunistic infections, see section 4.3) or severely immunocompromised patients (e.g. where levels of CD4 or CD8 are very low). Physicians should exercise caution when considering the use of MabThera in patients with a history ofrecurring or chronic infections or with underlying conditions which may further predispose patients to serious

infection, e.g. hypogammaglobulinaemia (see section 4.8). It is recommended that immunoglobulin levels are determined prior to initiating treatment with MabThera.

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

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

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

Hepatitis B virus (HBV) screening should be performed in all patients before initiation oftreatment with MabThera. At minimum this should include HBsAg-status and HBcAb-status. These can be complemented with other appropriate markers as per local guidelines. Patients with active hepatitis B disease should not be treated with MabThera. Patients with positive hepatitis B serology (either HBsAg or HBcAb) should consult liver disease experts before start oftreatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation.

Late neutropenia
Measure blood neutrophils prior to each course of MabThera, and regularly up to 6-months after cessation oftreatment, and upon signs or symptoms ofinfection (see section 4.8).

Skin reactions
Severe skin reactions such as Toxic Epidermal Necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome, some with fatal outcome, have been reported (see section 4.8). In case ofsuch an event with a suspected relationship to MabThera, treatment should be permanently discontinued.

Immunisation
Physicians should review the patient's vaccination status and patients should, ifpossible, be brought up-to-date with all immunisations in agreement with current immunisation guidelines prior to initiating MabThera therapy. Vaccination should be completed at least 4 weeks prior to first administration of MabThera.

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

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

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

Concomitant/sequential use of other DMARDs in rheumatoid arthritis
The concomitant use of MabThera and anti-rheumatic therapies other than those specified under the rheumatoid arthritis indication and posology is not recommended.

There are limited data from clinical trials to fully assess the safety ofthe sequential use ofother DMARDs (including TNF inhibitors and other biologics) following MabThera (see section 4.5). The available data indicate that the rate ofclinically relevant infection is unchanged when such therapies are used in patients previously treated with MabThera, however patients should be closely observed for signs ofinfection ifbiologic agents and/or DMARDs are used following MabThera therapy.

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

Excipients
This medicinal product contains 2.3 mmol (or 52.6 mg) sodium per 10 mL vial and 11.5 mmol (or 263.2 mg) sodium per 50 mL vial, equivalent to 2.6% (for 10ml vial) and 13.2% (for 50ml vial) ofthe WHO recommended maximum daily intake of2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms ofinteraction

Currently, there are limited data on possible drug interactions with MabThera.

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

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

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

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

4.6 Fertility, pregnancy and lactation

Contraception in males and females

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

Pregnancy

IgG immunoglobulins are known to cross the placental barrier.

B cell levels in human neonates following maternal exposure to MabThera have not been studied in clinical trials. There are no adequate and well-controlled data from studies in pregnant women, however transient B-cell depletion and lymphocytopenia have been reported in some infants born to mothers exposed to MabThera during pregnancy. Similar effects have been observed in animal studies (see section 5.3). For these reasons MabThera should not be administered to pregnant women unless the possible benefit outweighs the potential risk.

Breast-feeding

Limited data on rituximab excretion into breast milk suggest very low milk levels (relative infant dose less than 0.4%). Few cases of follow-up ofbreastfed infants describe normal growth and development up to 1.5 years. However, as these data are limited and the long-term outcomes of breastfed infants remain unknown, breastfeeding is not recommended while being treated with rituximab and optimally for 12 months following rituximab treatment.

Fertility

Animal studies did not reveal deleterious effects ofrituximab on reproductive organs.

4.7 Effects on ability to drive and use machines

No studies on the effects of MabThera on the ability to drive and use machines have been performed, although the pharmacological activity and adverse reactions reported to date suggest that MabThera would have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

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

Summary of the safety profile

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

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

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

The most frequently reported or observed serious adverse reactions were:

- IRRs (including cytokine-release syndrome, tumour-lysis syndrome), see section 4.4.
- Infections, see section 4.4.
- Cardiovascular events, see section 4.4.

Other serious ADRs reported include hepatitis B reactivation and PML (see section 4.4.).

Tabulated list of adverse reactions

The frequencies of ADRs reported with MabThera alone or in combination with chemotherapy are summarised in Table 3. Frequencies are defined as very common (³ 1/10), common (³ 1/100 to < 1/10), uncommon (³ 1/1,000 to < 1/100), rare (³ 1/10,000 to < 1/1000), very rare (< 1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in the order ofdecreasing seriousness.

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

Table 3 ADRs reported in clinical trials or during postmarketing surveillance in patients with NHL and CLL disease treated with MabThera monotherapy/maintenance or in combination with chemotherapy

MedDRA System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not known
Infections and infestations	bacterial infections, viral infections, +bronchitis	sepsis, +pneumonia, +febrile infection, +herpes zoster, +respiratory tract infection, fungal infections, infections of unknown aetiology, +acute bronchitis, +sinusitis, hepatitis B[1]		serious viral infection[2] Pneumocystis jirovecii	PML	
Blood and lymphatic system disorders	neutropenia, leucopenia, +febrile neutropenia, +thrombocytopenia	anaemia, +pancytopenia, +granulocytopenia	coagulation disorders, aplastic anaemia, haemolytic anaemia, lymphadenopathy		transient increase in serum IgM levels[3]	late neutropenia [3]
Immune system disorders	infusion-related reactions[4], angioedema	hypersensitivity		anaphylaxis	tumour lysis syndrome, cytokine release syndrome[4], serum sickness	infusion-related acute reversible thrombocytopenia[4]
Metabolism and nutrition disorders		hyperglycaemia, weight decrease, peripheral oedema, face oedema, increased LDH, hypocalcaemia				
Psychiatric disorders			depression, nervousness			
Nervous system disorders		paraesthesia, hypoaesthesia, agitation, insomnia, vasodilatation, dizziness, anxiety	dysgeusia		peripheral neuropathy, facial nerve palsy[5]	cranial neuropathy, loss of other senses[5]
Eye disorders		lacrimation disorder, conjunctivitis			severe vision loss[5]	
Ear and labyrinth disorders		tinnitus, ear pain				hearing loss[5]
Cardiac disorders		+myocardial infarction[4 and 6], arrhythmia, +atrial fibrillation, tachycardia, +cardiac disorder	+left ventricular failure, +supraventricular tachycardia, +ventricular tachycardia, +angina, +myocardial ischaemia, bradycardia	severe cardiac disorders [4 and 6]	heart failure[4 and 6]	
Vascular disorders		hypertension, orthostatic hypotension, hypotension			vasculitis (predominately cutaneous), leukocytoclastic vasculitis	

MedDRA System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not known
Respiratory, thoracic and mediastinal disorders		Bronchospasm[4], respiratory disease, chest pain, dyspnoea, increased cough, rhinitis	asthma, bronchiolitis obliterans, lung disorder, hypoxia	interstitial lung disease[7]	respiratory failure[4]	lung infiltration
Gastrointestinal disorders	nausea	vomiting, diarrhoea, abdominal pain, dysphagia, stomatitis, constipation, dyspepsia, anorexia, throat irritation	abdominal enlargement		gastro-intestinal perforation[7]	
Skin and subcutaneous tissue disorders	pruritus, rash, [+]alopecia	urticaria, sweating, night sweats, [+]skin disorder			severe bullous skin reactions, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome)[7]	
Musculoskeletal, connective tissue disorders		hypertonia, myalgia, arthralgia, back pain, neck pain, pain				
Renal and urinary disorders					renal failure[4]	
General disorders and administration site conditions	fever, chills, asthenia, headache	tumour pain, flushing, malaise, cold syndrome, [+]fatigue, [+]shivering, [+]multi-organ failure[4]	infusion site pain			
Investigations	decreased IgG levels					

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

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

[2] see also section infection below

[3] see also section haematologic adverse reactions below

[4] see also section infusionrelated reactions below. Rarely fatal cases reported

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

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

[7] includes fatal cases

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

Signs and symptoms suggestive ofan infusion-related reaction were reported in more than 50% of patients in clinical trials, and were predominantly seen during the first infusion, usually in the first one to two hours. These symptoms mainly comprised fever, chills and rigors. Other symptoms included flushing, angioedema, bronchospasm, vomiting, nausea, urticaria/rash, fatigue, headache, throat irritation, rhinitis, pruritus, pain, tachycardia, hypertension, hypotension, dyspnoea, dyspepsia,

asthenia and features oftumour lysis syndrome. Severe infusion-related reactions (such as bronchospasm, hypotension) occurred in up to 12% ofthe cases.

Additional reactions reported in some cases were myocardial infarction, atrial fibrillation, pulmonary oedema and acute reversible thrombocytopenia. Exacerbations ofpre-existing cardiac conditions such as angina pectoris or congestive heart failure or severe cardiac disorders (heart failure, myocardial infarction, atrial fibrillation), pulmonary oedema, multi-organ failure, tumour lysis syndrome, cytokine release syndrome, renal failure, and respiratory failure were reported at lower or unknown frequencies. The incidence ofinfusion-related symptoms decreased substantially with subsequent infusions and is <1% ofpatients by the eighth cycle ofMabThera (containing) treatment.

Description ofselected adverse reactions

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

Localised candida infections as well as Herpes zoster were reported at a higher incidence in the MabThera-containing arm ofrandomised studies. Severe infections were reported in about 4% of patients treated with MabThera monotherapy. Higher frequencies ofinfections overall, including grade 3 or 4 infections, were observed during MabThera maintenance treatment up to 2 years when compared to observation. There was no cumulative toxicity in terms ofinfections reported over a 2-year treatment period. In addition, other serious viral infections either new, reactivated or exacerbated, some ofwhich were fatal, have been reported with MabThera treatment. The majority of patients had received MabThera in combination with chemotherapy or as part ofa haematopoetic stem cell transplant. Examples ofthese serious viral infections are infections caused by the herpes viruses (Cytomegalovirus, Varicella Zoster Virus and Herpes Simplex Virus), JC virus (progressive multifocal leukoencephalopathy (PML)) and hepatitis C virus. Cases of fatal PML that occurred after disease progression and retreatment have also been reported in clinical trials. Cases ofhepatitis B reactivation, have been reported, the majority ofwhich were in patients receiving MabThera in combination with cytotoxic chemotherapy. In patients with relapsed/refractory CLL, the incidence ofgrade 3/4 hepatitis B infection (reactivation and primary infection) was 2% in R-FC vs 0% FC. Progression of Kaposi's sarcoma has been observed in MabThera-exposed patients with pre-existing Kaposi's sarcoma. These cases occurred in non-approved indications and the majority ofpatients were HIV positive.

Haematologic adverse reactions
In clinical trials with MabThera monotherapy given for 4 weeks, haematological abnormalities occurred in a minority ofpatients and were usually mild and reversible. Severe (grade 3/4) neutropenia was reported in 4.2%, anaemia in 1.1% and thrombocytopenia in 1.7% ofthe patients. During MabThera maintenance treatment for up to 2 years, leucopenia (5% vs. 2%, grade 3/4) and neutropenia (10% vs. 4%, grade 3/4) were reported at a higher incidence when compared to observation. The incidence ofthrombocytopenia was low (<1%, grade 3/4) and was not different between treatment arms. During the treatment course in studies with MabThera in combination with chemotherapy, grade 3/4 leucopenia (R-CHOP 88% vs. CHOP 79%, R-FC 23% vs. FC 12%), neutropenia (R-CVP 24% vs. CVP 14%; R-CHOP 97% vs. CHOP 88%, R-FC 30% vs. FC 19% in previously untreated CLL), pancytopenia (R-FC 3% vs. FC 1% in previously untreated CLL) were usually reported with higher frequencies when compared to chemotherapy alone. However, the higher incidence ofneutropenia in patients treated with MabThera and chemotherapy was not associated with a higher incidence ofinfections and infestations compared to patients treated with chemotherapy alone. Studies in previously untreated and relapsed/refractory CLL have established that in up to 25% ofpatients treated with R-FC neutropenia was prolonged (defined as neutrophil count remaining below $1x10^9$/L between day 24 and 42 after the last dose) or occurred with a late onset (defined as neutrophil count below $1x10^9$/L later than 42 days after last dose in patients with no previous prolonged neutropenia or who recovered prior to day 42) following treatment with MabThera plus FC. There were no differences reported for the incidence ofanaemia. Some cases oflate neutropenia occurring more than four weeks after the last infusion ofMabThera were reported. In the CLL first-line study, Binet stage C patients experienced more adverse events in the R-FC arm compared to

the FC arm (R-FC 83% vs. FC 71%). In the relapsed/refractory CLL study grade 3/4 thrombocytopenia was reported in 11% ofpatients in the R-FC group compared to 9% ofpatients in the FC group.

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

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

Respiratorysystem
Cases ofinterstitial lung disease, some with fatal outcome have been reported.

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

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

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

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

proportion ofpatients with IgG levels below the LLN was about 60% in the MabThera group throughout the 2 year treatment period, while it decreased in the observation group (36% after 2 years).

A small number ofspontaneous and literature cases ofhypogammaglobulinaemia have been observed in paediatric patients treated with MabThera, in some cases severe and requiring long-term immunoglobulin substitution therapy. The consequences oflong term B cell depletion in paediatric patients are unknown.

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

Patient subpopulations - MabThera monotherapy
Elderly (³ 65 years):
The incidence of ADRs ofall grades and grade 3/4 ADR was similar in elderly patients compared to younger patients (<65 years).

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

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

Patient subpopulations - MabThera combination therapy
Elderly (³ 65 years)
The incidence ofgrade 3/4 blood and lymphatic adverse events was higher in elderly patients compared to younger patients (<65 years), with previously untreated or relapsed/refractory CLL.

Experience from paediatric DLBCL/BL/BAL/BLL

Summary of safety profile

A multicenter, open-label randomized study of Lymphome Malin B chemotherapy (LMB) with or without MabThera was conducted in paediatric patients (aged ≥ 6 months to < 18 years old) with previously untreated advanced stage CD20 positive DLBCL/BL/BAL/BLL.

A total of 309 paediatric patients received MabThera and were included in the safety analysis population. Paediatric patients randomized to the LMB chemotherapy arm with MabThera, or enrolled in the single arm part ofthe study, were administered MabThera at a dose of 375mg/m2 BSA and received a total ofsix IV infusions of MabThera (two during each ofthe two induction courses and one during each ofthe two consolidation courses ofthe LMB scheme).

The safety profile of MabThera in paediatric patients (aged ≥ 6 months to < 18 years old) with previously untreated advanced stage CD20 positive DLBCL/BL/BAL/BLL was generally consistent in type, nature and severity with the known safety profile in adult NHL and CLL patients. Addition of MabThera to chemotherapy did result in an increased risk ofsome events including infections (including sepsis) compared to chemotherapy only.

Experience from rheumatoid arthritis

Summary of the safety profile

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

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

Patients received 2 x 1000 mg of MabThera separated by an interval oftwo weeks; in addition to methotrexate (10-25 mg/week). MabThera infusions were administered after an intravenous infusion of100 mg methylprednisolone; patients also received treatment with oral prednisone for 15 days.

Tabulated list of adverse reactions

Adverse reactions are listed in Table 4. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), and very rare (<1/10,000). Within each frequency grouping, undesirable effects are presented in order ofdecreasing seriousness.

The most frequent adverse reactions considered due to receipt of MabThera were IRRs. The overall incidence of IRRs in clinical trials was 23% with the first infusion and decreased with subsequent infusions. Serious IRRs were uncommon (0.5% ofpatients) and were predominantly seen during the initial course. In addition to adverse reactions seen in RA clinical trials for MabThera, progressive multifocal leukoencephalopathy (PML) (see section 4.4) and serum sickness-like reaction have been reported during post marketing experience.

Table 4 Summary ofadverse reactions reported in clinical trials or during postmarketing surveillance occurring in patients with rheumatoid arthritis receiving MabThera

MedDRA System Organ Class	Very Common	Common	Uncommon	Rare	Very rare
Infections and infestations	upper respiratory tract infection, urinary tract infections	bronchitis, sinusitis, gastroenteritis, tinea pedis			PML, reactivation of hepatitis B
Blood and lymphatic system disorders		neutropenia[1]		late neutropenia[2]	serum sickness-like reaction
Immune system disorders	[3]infusion-related reactions (hypertension, nausea, rash, pyrexia, pruritus, urticaria, throat irritation, hot flush, hypotension, rhinitis, rigors, tachycardia, fatigue, oropharyngeal pain, peripheral oedema, erythema)		[3]infusion related reactions (generalized oedema, bronchospasm, wheezing, laryngeal oedema, angioneurotic oedema, generalized pruritus, anaphylaxis, anaphylactoid reaction)		
General disorders and administration site conditions					
Metabolism and nutrition disorders		Hypercholesterolemia			
Psychiatric disorders		depression, anxiety			
Nervous system disorders	headache	paraesthesia, migraine, dizziness, sciatica			

MedDRA System Organ Class	Very Common	Common	Uncommon	Rare	Very rare
Cardiac disorders				angina pectoris, atrial fibrillation, heart failure, myocardial infarction	atrial flutter
Gastrointestinal disorders		dyspepsia, diarrhoea, gastro-oesophageal reflux, mouth ulceration, upper abdominal pain			
Skin and subcutaneous tissue disorders		alopecia			toxic epidermal necrolysis (Lyell's syndrome), Stevens-Johnson syndrome[5]
Musculo skeletal disorders and connective tissue disorders		arthralgia / musculoskeletal pain, osteoarthritis, bursitis			
Investigations	decreased IgM levels[4]	decreased IgG levels[4]			

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

Multiple courses

Multiple courses of treatment are associated with a similar ADR profile to that observed following first exposure. The rate of all ADRs following first MabThera exposure was highest during the first 6 months and declined thereafter. This is mostly accounted for by IRRs (most frequent during the first treatment course), RA exacerbation and infections, all of which were more frequent in the first 6 months of treatment.

Description of selected adverse reactions

Infusion-related reactions

The most frequent ADRs following receipt of MabThera in clinical studies were IRRs (refer to Table 4). Among the 3189 patients treated with MabThera, 1135 (36%) experienced at least one IRR with 733/3189 (23%) of patients experiencing an IRR following first infusion of the first exposure to MabThera. The incidence of IRRs declined with subsequent infusions. In clinical trials fewer than 1% (17/3189) of patients experienced a serious IRR. There were no CTC Grade 4 IRRs and no deaths due to IRRs in the clinical trials. The proportion of CTC Grade 3 events and of IRRs leading to withdrawal decreased by course and were rare from course 3 onwards. Premedication with intravenous glucocorticoid significantly reduced the incidence and severity of IRRs (see sections 4.2 and 4.4). Severe IRRs with fatal outcome have been reported in the post-marketing setting.

In a trial designed to evaluate the safety of a more rapid MabThera infusion in patients with rheumatoid arthritis, patients with moderate-to-severe active RA who did not experience a serious IRR during or within 24 hours of their first studied infusion were allowed to receive a 2-hour intravenous infusion of MabThera. Patients with a history of a serious infusion reaction to a biologic therapy for RA were excluded from entry. The incidence, types and severity of IRRs were consistent with that observed historically. No serious IRRs were observed.

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

Cases ofprogressive multifocal leukoencephalopathy with fatal outcome have been reported following use ofMabThera for the treatment ofautoimmune diseases. This includes rheumatoid arthritis and off-label autoimmune diseases, including Systemic Lupus Erythematosus (SLE) and vasculitis.

In patients with non-Hodgkin's lymphoma receiving MabThera in combination with cytotoxic chemotherapy, cases ofhepatitis B reactivation have been reported (see non-Hodgkin's lymphoma). Reactivation ofhepatitis B infection has also been very rarely reported in RA patients receiving MabThera (see Section 4.4).

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

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

Neutropenia
Events ofneutropenia were observed with MabThera treatment, the majority ofwhich were transient and mild or moderate in severity. Neutropenia can occur several months after the administration of MabThera (see section 4.4).

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

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

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

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

A small number ofspontaneous and literature cases ofhypogammaglobulinaemia have been observed in paediatric patients treated with MabThera, in some cases severe and requiring long-term immunoglobulin substitution therapy. The consequences oflong-term B cell depletion in paediatric patients are unknown.

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

Adult induction of remission (GPA/MPA Study 1)
In GPA/MPA Study 1, 99 adult patients were treated for induction of remission of GPA and MPA with MabThera (375 mg/m^2, once weekly for 4 weeks) and glucocorticoids (see section 5.1*).*

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

Table 5 Adverse reactions occurring at 6-months in ≥ 5% of adult patients receiving MabThera in GPA/MPA Study 1, and at a higher frequency than the comparator group.

MedDRA System organ class Adverse reaction	Rituximab (n=99)
Infections and infestations	
Urinary tract infection	7%
Bronchitis	5%
Herpes zoster	5%
Nasopharyngitis	5%
Blood and lymphatic system disorder	
Thrombocytopenia	7%
Immune system disorders	
Cytokine release syndrome	5%
Metabolism and nutrition disorders	
Hyperkalaemia	5%
Psychiatric disorders	
Insomnia	14%
Nervous system disorders	
Dizziness	10%
Tremor	10%
Vascular disorders	
Hypertension	12%
Flushing	5%
Respiratory, thoracic and mediastinal disorders	
Cough	12%
Dyspnoea	11%
Epistaxis	11%
Nasal congestion	6%
Gastrointestinal disorders	
Diarrhoea	18%
Dyspepsia	6%
Constipation	5%
Skin and subcutaneous tissue disorders	
Acne	7%
Musculoskeletal and connective tissue disorders	
Muscle spasms	18%

Arthralgia	15%

MedDRA System organ class Adverse reaction	Rituximab (n=99)
Back pain	10%
Muscle weakness	5%
Musculoskeletal pain	5%
Pain in extremities	5%
General disorders and administration site conditions	
Peripheral oedema	16%
Investigations	
Decreased haemoglobin	6%

Adult maintenance treatment (GPA/MPA Study 2)

In GPA/MPA Study 2, a total of 57 adult patients with severe, active GPA and MPA were treated with MabThera for the maintenance ofremission (see section 5.1).

Table 6 Adverse reactions occurring in ≥ 5% of adult patients receiving MabThera in GPA/MPA Study 2, and at a higher frequency than the comparator group

MedDRA System Organ Class Adverse reaction	Rituximab (n=57)
Infections and infestations	
Bronchitis	14%
Rhinitis	5%
Respiratory, thoracic and mediastinal disorders	
Dyspnoea	9%
Gastrointestinal disorders	
Diarrhoea	7%
General disorders and administration site conditions	
Pyrexia	9%
Influenza-like illness	5%
Oedema peripheral	5%
Injury, poisoning and procedural complications	
Infusion-related reactions[1]	12%
[1]Details on infusion related reactions are provided in the description ofselected adverse reactions section.	

The overall safety profile was consistent with the well-established safety profile for MabThera in approved autoimmune indications, including GPA/MPA. Overall, 4% ofpatients in the MabThera arm experienced adverse events leading to discontinuation. Most adverse events in the MabThera arm were mild or moderate in intensity. No patients in the MabThera arm had fatal adverse events.

The most commonly reported events considered as ADRs were infusion-related reactions and infections.

Long-term follow-up (GPA/MPA Study 3)

In a long-term observational safety study, 97 GPA/MPA patients received treatment with MabThera (mean of 8 infusions [range 1-28]) for up to 4 years, according to their physician's standard practice and discretion. The overall safety profile was consistent with the well-established safety profile of MabThera in RA and GPA/MPA and no new adverse reactions were reported.

Paediatric population
An open-label, single arm study was conducted in 25 paediatric patients with severe, active GPA or MPA. The overall study period consisted ofa 6-month remission induction phase with a minimum 18-month follow-up, up to 4.5 years overall. During the follow-up phase, MabThera was given at the discretion ofthe investigator (17 out of25 patients received additional MabThera treatment). Concomitant treatment with other immunosuppressive therapy was permitted (see section 5.1).

ADRs were considered as adverse events that occurred at an incidence of≥ 10%. These included: infections (17 patients [68%] in the remission induction phase; 23 patients [92%] in the overall study period), IRRs (15 patients [60%] in the remission induction phase; 17 patients [68%] in the overall study period), and nausea (4 patients [16%] in the remission induction phase; 5 patients [20%] in the overall study period).

During the overall study period, the safety profile of MabThera was consistent with that reported during the remission induction phase.

The safety profile of MabThera in paediatric GPA or MPA patients was consistent in type, nature and severity with the known safety profile in adult patients in the approved autoimmune indications, including adult GPA or MPA.

Description of selected adverse reactions

Infusion-related reactions
In GPA/MPA Study 1 (adult induction ofremission study), IRRs were defined as any adverse event occurring within 24 hours ofan infusion and considered to be infusion-related by investigators in the safety population. Ofthe 99 patients treated with MabThera, 12 (12%) experienced at least one IRR. All IRRs were CTC Grade 1 or 2. The most common IRRs included cytokine release syndrome, flushing, throat irritation, and tremor. MabThera was given in combination with intravenous glucocorticoids which may reduce the incidence and severity ofthese events.

In GPA/MPA Study 2 (adult maintenance study), 7/57 (12%) patients in the MabThera arm experienced at least one infusion-related reaction. The incidence of IRR symptoms was highest during or after the first infusion (9%) and decreased with subsequent infusions (<4%). All IRR symptoms were mild or moderate and most ofthem were reported from the SOCs Respiratory, Thoracic and Mediastinal Disorders and Skin and Subcutaneous Tissue disorders.

In the clinical trial in paediatric patients with GPA or MPA, the reported IRRs were predominantly seen with the first infusion (8 patients [32%]), and then decreased over time with the number of MabThera infusions (20% with the second infusion, 12% with the third infusion and 8% with the fourth infusion). The most common IRR symptoms reported during the remission induction phase were: headache, rash, rhinorrhea and pyrexia (8%, for each symptom). The observed symptoms ofIRRs were similar to those known in adult GPA or MPA patients treated with MabThera. The majority of IRRs were Grade 1 and Grade 2, there were two non-serious Grade 3 IRRs, and no Grade 4 or 5 IRRs reported. One serious Grade 2 IRR (generalized oedema which resolved with treatment) was reported in one patient (see section 4.4).

Infections
In GPA/MPA Study 1, the overall rate ofinfection was approximately 237 per 100 patient years (95% CI 197 - 285) at the 6-month primary endpoint. Infections were predominately mild to moderate and consisted mostly ofupper respiratory tract infections, herpes zoster and urinary tract infections. The rate ofserious infections was approximately 25 per 100 patient years. The most frequently reported serious infection in the MabThera group was pneumonia at a frequency of4%.

In GPA/MPA Study 2, 30/57 (53%) patients in the MabThera arm experienced infections. The incidence ofall grade infections was similar between the arms. Infections were predominately mild to moderate. The most common infections in the MabThera arm included upper respiratory tract infections, gastroenteritis, urinary tract infections and herpes zoster. The incidence ofserious

infections was similar in both arms (approximately 12%). The most commonly reported serious infection in the MabThera group was mild or moderate bronchitis.

In the clinical trial in paediatric patients with severe, active GPA and MPA, 91% ofreported infections were non-serious and 90% were mild to moderate.

The most common infections in the overall phase were: upper respiratory tract infections (URTIs) (48%), influenza (24%), conjunctivitis (20%), nasopharyngitis (20%), lower respiratory tract infections (16%), sinusitis (16%), viral URTIs (16%), ear infection (12%), gastroenteritis (12%), pharyngitis (12%), urinary tract infection (12%). Serious infections were reported in 7 patients (28%), and included: influenza (2 patients [8%]) and lower respiratory tract infection (2 patients [8%]) as the most frequently reported events.

Malignancies
In GPA/MPA Study 1, the incidence ofmalignancy in MabThera treated patients in the GPA and MPA clinical study was 2.00 per 100 patient years at the study common closing date (when the final patient had completed the follow-up period). On the basis ofstandardised incidence ratios, the incidence ofmalignancies appears to be similar to that previously reported in patients with ANCA-associated vasculitis.

In the paediatric clinical trial, no malignancies were reported with a follow-up period ofup to 54 months.

Cardiovascular adverse reactions
In GPA/MPA Study 1, cardiac events occurred at a rate ofapproximately 273 per 100 patient years (95% CI 149-470) at the 6-month primary endpoint. The rate ofserious cardiac events was 2.1 per 100 patient years (95% CI 3 -15). The most frequently reported events were tachycardia (4%) and atrial fibrillation (3%) (see section 4.4).

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

Hepatitis-B reactivation
A small number ofcases ofhepatitis-B reactivation, some with fatal outcome, have been reported in granulomatosis with polyangiitis and microscopic polyangiitis patients receiving MabThera in the postmarketing setting.

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

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

In GPA/MPA Study 2, no clinically meaningful di**f** erences between the two treatment arms or decreases in total immunoglobulin, IgG, IgM or IgA levels were observed throughout the trial.

In the paediatric clinical trial, during the overall study period, 3/25 (12%) patients reported an event of hypogammaglobulinaemia, 18 patients (72%) had prolonged (defined as Ig levels below lower limit of normal for at least 4 months) low IgG levels (ofwhom 15 patients also had prolonged low IgM).

Three patients received treatment with intravenous immunoglobulin (IV-IG). Based on limited data, no firm conclusions can be drawn regarding whether prolonged low IgG and IgM led to an increased risk ofserious infection in these patients. The consequences oflong term B cell depletion in paediatric patients are unknown.

Neutropenia
In GPA/MPA Study 1, 24% ofpatients in the MabThera group (single course) and 23% ofpatients in the cyclophosphamide group developed CTC grade 3 or greater neutropenia. Neutropenia was not associated with an observed increase in serious infection in MabThera-treated patients.

In GPA/MPA Study 2, the incidence ofall-grade neutropenia was 0% for MabThera-treated patients vs 5% for azathioprine treated patients.

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

Experience from pemphigus vulgaris

Summary ofthe safety profile in PV Study 1 (Study ML22196) and PV Study 2 (Study WA29330)
The safety profile of MabThera in combination with short-term, low-dose glucocorticoids in the treatment ofpatients with pemphigus vulgaris was studied in a Phase 3, randomised, controlled, multicenter, open-label study in pemphigus patients that included 38 pemphigus vulgaris (PV) patients randomised to the MabThera group (PV Study 1). Patients randomised to the MabThera group received an initial 1000 mg IV on Study Day 1 and a second 1000 mg IV on Study Day 15. Maintenance doses of500 mg IV were administered at months 12 and 18. Patients could receive 1000 mg IV at the time ofrelapse (see section 5.1).

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

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

Tabulated list ofadverse reactions for PV Studies 1 and 2
Adverse reactions from PV Studies 1 and 2 are presented in Table 7. In PV Study 1, ADRs were defined as adverse events which occurred at a rate of³ 5% among MabThera-treated PV patients, with a ³ 2% absolute di**f** erence in incidence between the MabThera-treated group and the standard-dose prednisone group up to month 24. No patients were withdrawn due to ADRs in Study 1. In PV Study 2, ADRs were defined as adverse events occurring in ≥5% ofpatients in the MabThera arm and assessed as related.

Table 7 Adverse reactions in MabThera-treated pemphigus vulgaris patients in PV Study 1 (up to Month 24) and PV Study 2 (up to Week 52)

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

Description of selected adverse reactions

Infusion-related reactions

In PV Study 1, infusion-related reactions were common (58%). Nearly all infusion-related reactions were mild to moderate. The proportion ofpatients experiencing an infusion- related reaction was 29% (11 patients), 40% (15 patients), 13% (5 patients), and 10% (4 patients) following the first, second, third, and fourth infusions, respectively. No patients were withdrawn from treatment due to infusion-related reactions. Symptoms ofinfusion-related reactions were similar in type and severity to those seen in RA and GPA/MPA patients.

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

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

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

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

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

Reporting ofsuspected adverse reactions
Reporting suspected adverse reactions after authorisation ofthe medicinal product is important. It allows continued monitoring ofthe benefit/risk balance ofthe medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Limited experience with doses higher than the approved dose ofintravenous MabThera formulation is available from clinical trials in humans. The highest intravenous dose of MabThera tested in humans to date is 5000 mg (2250 mg/m^2), tested in a dose escalation study in patients with CLL. No additional safety signals were identified.

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

In the postmarketing setting five cases of MabThera overdose have been reported. Three cases had no reported adverse event. The two adverse events that were reported were flu-like symptoms, with a dose of1.8 g ofrituximab and fatal respiratory failure, with a dose of2 g ofrituximab.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

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

The Fab domain ofrituximab binds to the CD20 antigen on B lymphocytes and the Fc domain can recruit immune effector functions to mediate B cell lysis. Possible mechanisms ofeffector-mediated cell lysis include complement-dependent cytotoxicity (CDC) resulting from C1q binding, and antibody-dependent cellular cytotoxicity (ADCC) mediated by one or more ofthe Fcg receptors on the surface ofgranulocytes, macrophages and NK cells. Rituximab binding to CD 20 antigen on B lymphocytes has also been demonstrated to induce cell death via apoptosis.

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

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

Follicularlymphoma

Monotherapy

Initial treatment, weekly for 4 doses
In the pivotal trial, 166 patients with relapsed or chemoresistant low-grade or follicular B cell NHL received 375 mg/m^2 of MabThera as an intravenous infusion once weekly for four weeks. The overall response rate (ORR) in the intent-to-treat (ITT) population was 48 % (CI_{95}% 41% - 56%) with a 6% complete response (CR) and a 42 % partial response (PR) rate. The projected median time to progression (TTP) for responding patients was 13.0 months. In a subgroup analysis, the ORR was higher in patients with IWF B, C, and D histological subtypes as compared to IWF A subtype (58 % vs. 12%), higher in patients whose largest lesion was < 5 cm vs. > 7 cm in greatest diameter (53% vs. 38%), and higher in patients with chemosensitive relapse as compared to chemoresistant (defined as duration ofresponse < 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 ofbulky disease, normal or high LDH nor presence ofextranodal 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% ofpatients with bone marrow involvement responded compared to 59% ofpatients with no bone marrow involvement (p=0.0186). This finding was not supported by a stepwise logistic regression analysis in which the following factors were identified as prognostic factors: histological type, bcl-2 positivity at baseline, resistance to last chemotherapy and bulky disease.

Initial treatment, weekly for 8 doses
In a multi-centre, single-arm trial, 37 patients with relapsed or chemoresistant, low grade or follicular B cell NHL received 375 mg/m^2 of MabThera as intravenous infusion weekly for eight doses. The ORR was 57% (95% Confidence interval (CI); 41% – 73%; CR 14%, PR 43%) with a projected median TTP for responding patients of 19.4 months (range 5.3 to 38.9 months).

Initial treatment, bulky disease, weekly for 4 doses
In pooled data from three trials, 39 patients with relapsed or chemoresistant, bulky disease (single lesion ³ 10 cm in diameter), low grade or follicular B cell NHL received 375 mg/m2 of MabThera as intravenous infusion weekly for four doses. The ORR was 36 % (CI_{95}% 21% – 51%; CR 3%, PR 33%) with a median TTP for responding patients of 9.6 months (range 4.5 to 26.8 months).

Re-treatment, weekly for 4 doses
In a multi-centre, single-arm trial, 58 patients with relapsed or chemoresistant low grade or follicular B cell NHL, who had achieved an objective clinical response to a prior course of MabThera, were re-treated with 375 mg/m^2 of MabThera as intravenous infusion weekly for four doses. Three of the patients had received two courses of MabThera before enrolment and thus were given a third course in the study. Two patients were re-treated twice in the study. For the 60 re-treatments on study, the ORR was 38% (CI_{95}% 26% – 51%; 10% CR, 28% PR) with a projected median TTP for responding patients of 17.8 months (range 5.4 – 26.6). This compares favourably with the TTP achieved after the prior course of MabThera (12.4 months).

Initial treatment, in combination with chemotherapy

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

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

Results from three other randomised trials using MabThera in combination with chemotherapy regimen other than CVP (CHOP, MCP, CHVP/Interferon-α) have also demonstrated significant improvements in response rates, time-dependent parameters as well as in overall survival. Key results from all four studies are summarised in Table 8.

Table 8 Summary of key results from four phase III randomised studies evaluating the benefit of MabThera with different chemotherapy regimens in follicular lymphoma

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

EFS – Event Free Survival
TTP – Time to progression or death
PFS – Progression-Free Survival
TTF – Time to Treatment Failure
OS rates – survival rates at the time of the analyses

Maintenance therapy

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

The pre-specified primary analysis was conducted at a median observation time of 25 months from randomization, maintenance therapy with MabThera resulted in a clinically relevant and statistically significant improvement in the primary endpoint of investigator assessed progression-free survival (PFS) as compared to observation in patients with previously untreated follicular lymphoma (Table 9).

Significant benefit from maintenance treatment with MabThera was also seen for the secondary endpoints event-free survival (EFS), time to next anti-lymphoma treatment (TNLT) time to next chemotherapy (TNCT) and overall response rate (ORR) in the primary analysis (Table 9).

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

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

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

* at end ofmaintenance/observation; final analysis results based on median follow-up of73 months.
FU: follow-up; NR: not reached at time ofclinical cut off, TNCT: time to next chemotherapy treatment; TNLT: time to next anti lymphoma treatment.

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

Relapsed/Refractory follicular lymphoma

In a prospective, open label, international, multi-centre, phase III trial, 465 patients with relapsed/refractory follicular lymphoma were randomised in a first step to induction therapy with either CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone; n=231) or MabThera plus CHOP (R-CHOP, n=234). The two treatment groups were well balanced with regard to baseline characteristics and disease status. A total of 334 patients achieving a complete or partial remission following induction therapy were randomised in a second step to MabThera maintenance therapy (n=167) or observation (n=167). MabThera maintenance treatment consisted ofa single infusion of MabThera at 375 mg/m^2 body surface area given every 3 months until disease progression or for a maximum period oftwo years.

The final efficacy analysis included all patients randomised to both parts of the study. After a median observation time of 31 months for patients randomised to the induction phase, R-CHOP significantly improved the outcome of patients with relapsed/refractory follicular lymphoma when compared to CHOP (see Table 10).

Table 10 Induction phase: overview of efficacy results for CHOP vs. R-CHOP (31 months median observation time)

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

[1)] Estimates were calculated by hazard ratios

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

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

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

Table 11 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 ofinduction regimen (CHOP or R-CHOP) or quality ofresponse to induction treatment (CR or PR) (Table 11). MabThera maintenance treatment significantly prolonged median PFS in patients responding to CHOP induction therapy (median PFS 37.5 months vs. 11.6 months, p< 0.0001) as well as in those responding to R-CHOP induction (median PFS 51.9 months vs. 22.1 months, p=0.0071). Although subgroups were small, MabThera maintenance treatment provided a significant benefit in terms ofoverall survival for both patients responding to CHOP and patients responding to R-CHOP, although longer follow-up is required to confirm this observation.

Adult Diffuse large B cell non-Hodgkin's lymphoma

In a randomised, open-label trial, a total of 399 previously untreated elderly patients (age 60 to 80 years) with diffuse large B cell lymphoma received standard CHOP chemotherapy (cyclophosphamide 750 mg/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 ofthe treatment cycle.

The final efficacy analysis included all randomised patients (197 CHOP, 202 R-CHOP), and had a median follow-up duration ofapproximately 31 months. The two treatment groups were well balanced in baseline disease characteristics and disease status. The final analysis confirmed that R-CHOP treatment was associated with a clinically relevant and statistically significant improvement in the duration ofevent-free survival (the primary efficacy parameter; where events were death, relapse or progression oflymphoma, or institution ofa new anti-lymphoma treatment) (p=0.0001). Kaplan Meier estimates ofthe median duration ofevent-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 ofthe duration ofoverall 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 ofall secondary parameters (response rates, progression-free survival, disease-free survival, duration ofresponse) 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 ofdisease progression was reduced by 46% and the risk ofrelapse by 51%. In all patient subgroups (gender, age, age adjusted IPI, Ann Arbor stage, ECOG, β2 microglobulin, LDH, albumin, B symptoms, bulky disease, extranodal sites, bone marrow involvement), the risk ratios for event-free survival and overall survival (R-CHOP compared with CHOP) were less than 0.83 and 0.95 respectively. R-CHOP was associated with improvements in outcome for both high- and low-risk patients according to age adjusted IPI.

Clinical laboratory findings

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

Chronic lymphocytic leukaemia

In two open-label randomised trials, a total of 817 previously untreated patients and 552 patients with relapsed/refractory CLL were randomised to receive either FC chemotherapy (fludarabine 25 mg/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 ofeach subsequent treatment cycle. Patients were excluded from the study in relapsed/refractory CLL ifthey had previously been treated with monoclonal antibodies or ifthey were refractory (defined as failure to achieve a partial remission for at least 6 months) to fludarabine or any nucleoside analogue. A total of 810 patients (403 R-FC, 407 FC) for the first-line study (Table 12a and Table 12b) and 552 patients (276 R-FC, 276 FC) for the relapsed/refractory study (Table 13) were analysed for efficacy.

In the first-line study, after a median observation time of 48.1 months, the median PFS was 55 months in the R-FC group and 33 months in the FC group ($p < 0.0001$, log-rank test). The analysis of overall survival showed a significant benefit of R-FC treatment over FC chemotherapy alone ($p = 0.0319$, log-rank test) (Table 12a). The benefit in terms of PFS was consistently observed in most patient subgroups analysed according to disease risk at baseline (i.e. Binet stages A-C) (Table 12b).

Table 12a First-line treatment of chronic lymphocytic leukaemia

Overview of efficacy results for MabThera plus FC vs. FC alone - 48.1 months median observation time

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

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

Table 12b First-line treatment of chronic lymphocytic leukaemia

Hazard ratios of progression-free survival according to Binet stage (ITT) – 48.1 months median observation time

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

CI: Confidence Interval

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

Table 13 Treatment of relapsed/refractory chronic lymphocytic leukaemia - overview of efficacy results for MabThera plus FC vs. FC alone (25.3 months median observation time)

Efficacy Parameter	Kaplan-Meier Estimate of Median Time to Event (Months)			Risk Reduction
	FC (N = 276)	R-FC (N=276)	Log-Rank p value	
Progression-free survival (PFS)	20.6	30.6	0.0002	35%
Overall survival	51.9	NR	0.2874	17%
Event free survival	19.3	28.7	0.0002	36%
Response rate (CR, nPR, or PR)	58.0%	69.9%	0.0034	n.a.
CR rates	13.0%	24.3%	0.0007	n.a.
Duration ofresponse *	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 analysedusing Chi-squared Test.
*: only applicable to patients achieving a CR, nPR, PR; NR: not reached n.a. not applicable
**: only applicable to patients achieving a CR;

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

Paediatric population

A multicenter, open-label, randomized study of Lymphome Malin B (LMB) chemotherapy (corticosteroids, vincristine, cyclophosphamide, high-dose methotrexate, cytarabine, doxorubicin, etoposide and triple drug [methotrexate/cytarabine/ corticosteroid] intrathecal therapy) alone or in combination with MabThera was conducted in paediatric patients with previously untreated advanced stage CD20 positive DLBCL/BL/BAL/BLL. Advanced stage is defined as Stage III with elevated LDH level ("B-high"), [LDH > twice the institutional upper limit ofthe adult normal values (> Nx2)] or any stage IV or BAL. Patients were randomized to receive either LMB chemotherapy or six IV infusions of MabThera at a dose of 375mg/m^2 BSA in combination with LMB chemotherapy (two during each ofthe two induction courses and one during each ofthe two consolidation courses) as per the LMB scheme. A total of 328 randomized patients were included in the efficacy analyses, ofwhich one patient under 3 years ofage received MabThera in combination with LMB chemotherapy.

The two treatment arms, LMB (LMB chemotherapy) and R-LMB (LMB chemotherapy with MabThera), were well balanced with regards to baseline characteristics. Patients had a median age of 7 and 8 years in the LMB arm and R-LMB arm, respectively. Approximately halfofpatients were in Group B (50.6% in the LMB arm and 49.4% in the R-LMB arm), 39.6% in Group C1 in both arms, and 9.8% and 11.0% were in Group C3 in the LMB and R-LMB arms, respectively. Based on Murphy staging, most patients were either BL stage III (45.7% in the LMB arm and 43.3% in the R-LMB arm) or BAL, CNS negative (21.3% in the LMB arm and 24.4% in the R-LMB arm). Less than halfofthe patients (45.1% in both arms) had bone marrow involvement, and most patients (72.6% in the LMB arm and 73.2% in the R-LMB arm) had no CNS involvement. The primary efficacy endpoint was

EFS, where an event was defined as occurrence ofprogressive disease, relapse, second malignancy, death from any cause, or non-response as evidenced by detection ofviable cells in residue after the second CYVE course, whichever occurs first. The secondary e**f** icacy endpoints were OS and CR (complete remission).

At the pre-specified interim analysis with approximately 1 year ofmedian follow-up, clinically relevant improvement in the primary endpoint of EFS was observed, with 1-year rate estimates of 94.2% (95% CI, 88.5% - 97.2%) in the R-LMB arm vs. 81.5% (95% CI, 73.0% - 87.8%) in the LMB arm, and adjusted Cox HR 0.33 (95% CI, 0.14 – 0.79). Upon IDMC (independent data monitoring committee) recommendation based on this result, the randomization was halted and patients in the LMB arm were allowed to cross over to receive MabThera.

Primary efficacy analyses were performed in 328 randomized patients with a median follow-up of3.1 years. The results are described in Table 14.

Table 14: Overview of Primary E**f** icacy Results (ITT population)

Analysis	LMB (N = 164)	R-LMB (N=164)
EFS	28 events	10 events
	One-sided log-rank test p-value 0.0006	
	Adjusted Cox HR 0.32 (90% CI: 0.17, 0.58)	
3-year EFS rates	82.3% (95% CI: 75.7%, 87.5%)	93.9% (95% CI: 89.1%, 96.7%)
OS	20 deaths	8 deaths
	One-sided log-rank test p-value 0.0061	
	Adjusted Cox model HR 0.36 (95% CI: 0.16; 0.81)	
3-year OS rates	87.3% (95% CI: 81.2%, 91.6%)	95.1% (95% CI: 90.5%, 97.5%)
CR rate	93.6% (95% CI: 88.2%; 97.0%)	94.0% (95% CI: 88.8%, 97.2%)

The primary efficacy analysis showed an EFS benefit of MabThera addition to LMB chemotherapy over LMB chemotherapy alone, with an EFS HR 0.32 (90% CI 0.17 - 0.58) from a Cox regression analysis adjusting for national group, histology, and therapeutic group. While no major di**f** erences in numbers ofpatients achieving CR was observed between the two treatment groups, the benefit of MabThera addition to LMB chemotherapy was also shown in the secondary endpoint ofOS, with the OS HR of0.36 (95% CI, 0.16 – 0.81).

The European Medicines Agency has waived the obligation to submit the results ofstudies with MabThera in all subsets ofthe paediatric population with follicular lymphoma and CLL, and in the paediatric population from birth to < 6 months ofage in CD20 positive di**f** use large B-cell lymphoma. See Section 4.2 for information on paediatric use.

Clinical experience in rheumatoid arthritis

The e**f** icacy and safety of MabThera in alleviating the symptoms and signs ofrheumatoid arthritis in patients with an inadequate response to TNF-inhibitors was demonstrated in a pivotal randomised, controlled, double-blind, multicenter trial (Trial 1).

Trial 1 evaluated 517 patients that had experienced an inadequate response or intolerance to one or more TNF inhibitor therapies. Eligible patients had active rheumatoid arthritis, diagnosed according to the criteria ofthe American College of Rheumatology (ACR). MabThera was administered as two IV infusions separated by an interval of 15 days. Patients received 2 x 1000 mg intravenous infusions of MabThera or placebo in combination with MTX. All patients received concomitant 60 mg oral prednisone on days 2-7 and 30 mg on days 8-14 following the first infusion. The primary endpoint was the proportion ofpatients who achieved an ACR20 response at week 24. Patients were followed beyond week 24 for long term endpoints, including radiographic assessment at 56 weeks and at 104 weeks. During this time, 81% ofpatients, from the original placebo group received MabThera between weeks 24 and 56, under an open label extension study protocol.

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

Disease activity outcomes

MabThera in combination with methotrexate significantly increased the proportion ofpatients achieving at least a 20 % improvement in ACR score compared with patients treated with methotrexate alone (Table 15). Across all development studies the treatment benefit was similar in patients independent ofage, gender, body surface area, race, number ofprior treatments or disease status.

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

Table 15 Clinical response outcomes at primary endpoint in Trial 1(ITT population)

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

† Outcome at 24 weeks

Significant di**f** erence from placebo + MTX at the primary timepoint: ***$p \leq 0.0001$

Patients treated with MabThera in combination with methotrexate had a significantly greater reduction in disease activity score (DAS28) than patients treated with methotrexate alone (Table 15). Similarly, a good to moderate European League Against Rheumatism (EULAR) response was achieved by significantly more MabThera treated patients treated with MabThera and methotrexate compared to patients treated with methotrexate alone (Table 15).

Radiographic response

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

In Trial 1, conducted in patients with inadequate response or intolerance to one or more TNF inhibitor therapies, receiving MabThera in combination with methotrexate demonstrated significantly less radiographic progression than patients originally receiving methotrexate alone at 56 weeks. Ofthe patients originally receiving methotrexate alone, 81 % received MabThera either as rescue between

weeks 16-24 or in the extension trial, before week 56. A higher proportion ofpatients receiving the original MabThera/MTX treatment also had no erosive progression over 56 weeks (Table 16).

Table 16 Radiographic outcomes at 1 year (mITT population)

	Placebo+MTX	MabThera+MTX 2 × 1000 mg
Trial 1	(n = 184)	(n = 273)
Mean change from baseline:		
Modified total sharp score	2.30	1.01*
Erosion score	1.32	0.60*
Joint space narrowing score	0.98	0.41**
Proportion ofpatients with no radiographic change	46%	53%, NS
Proportion ofpatients with no erosive change	52%	60%, NS

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

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

Physical function and quality oflife outcomes

Significant reductions in disability index (HAQ-DI) and fatigue (FACIT-Fatigue) scores were observed in patients treated with MabThera compared to patients treated with methotrexate alone. The proportions of MabThera treated patients showing a minimal clinically important difference (MCID) in HAQ-DI (defined as an individual total score decrease of>0.22) was also higher than among patients receiving methotrexate alone (Table 17).

Significant improvement in health-related quality oflife was also demonstrated with significant improvement in both the physical health score (PHS) and mental health score (MHS) ofthe SF-36. Further, a significantly higher proportion ofpatients achieved MCIDs for these scores (Table 17).

Table 17 Physical function and quality oflife outcomes at week 24 in Trial 1

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

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

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

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

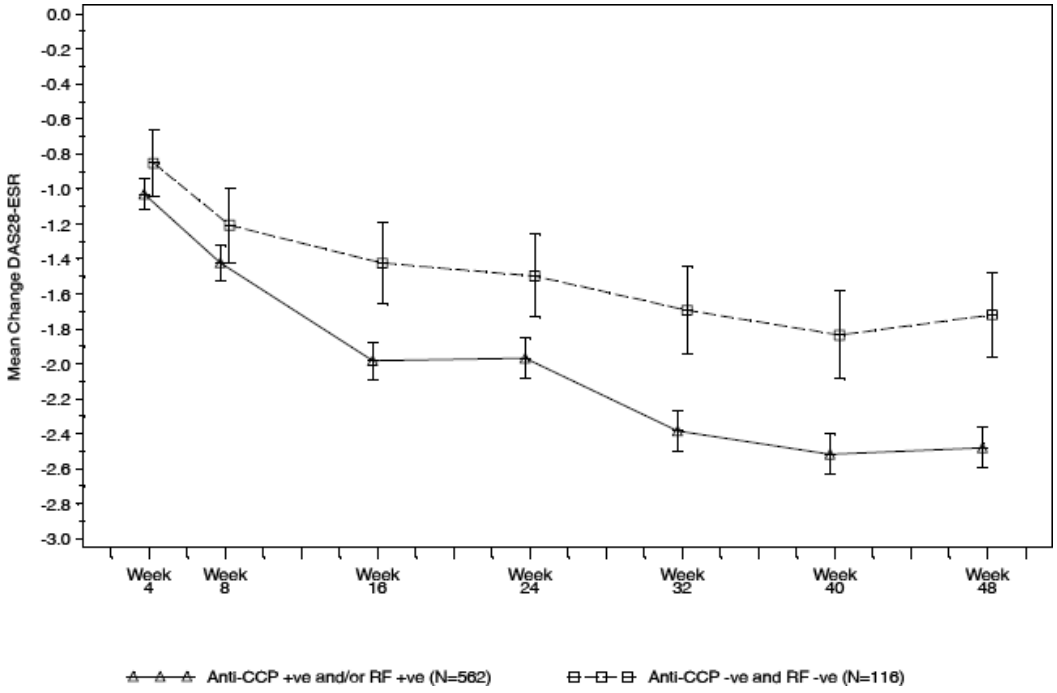
Efficacy outcomes in MabThera treated patients were analysed based on autoantibody status prior to commencing treatment. At Week 24, patients who were seropositive to RF and/or anti-CCP at baseline had a significantly increased probability ofachieving ACR20 and 50 responses compared to seronegative patients (p=0.0312 and p=0.0096) (Table 18). These findings were replicated at Week 48, where autoantibody seropositivity also significantly increased the probability ofachieving ACR70. At week 48 seropositive patients were 2-3 times more likely to achieve ACR responses compared to seronegative patients. Seropositive patients also had a significantly greater decrease in DAS28-ESR compared to seronegative patients (Figure 1).

Table 18 Summary ofefficacy by baseline autoantibody status

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

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

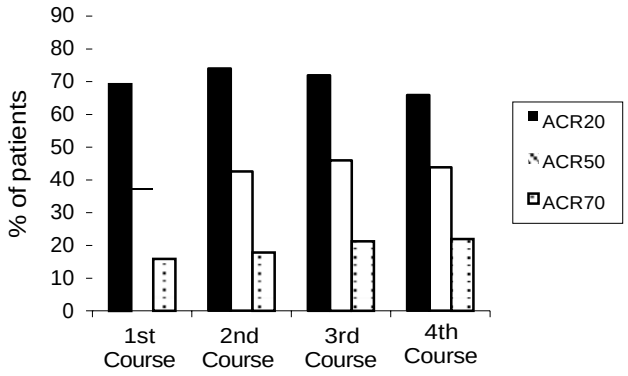
Figure 1: Change from baseline of DAS28-ESR by baseline autoantibody status



Long-term efficacy with multiple course therapy

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

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



Clinical laboratory findings

A total of 392/3095 (12.7%) patients with rheumatoid arthritis tested positive for ADAin clinical studies following therapy with MabThera. The emergence of ADAwas not associated with clinical deterioration or with an increased risk ofreactions to subsequent infusions in the majority ofpatients. The presence of ADA may be associated with worsening ofinfusion or allergic reactions after the second infusion ofsubsequent courses.

Paediatric population

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

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

Adult induction of remission

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

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

The primary outcome measure was achievement ofcomplete remission at 6 months defined as a Birmingham Vasculitis Activity Score for Wegener's granulomatosis (BVAS/WG) of 0, and off glucocorticoid therapy. The prespecified non-inferiority margin for the treatment di**f** erence was 20%. The trial demonstrated non-inferiority ofMabThera to cyclophosphamide for complete remission (CR) at 6 months (Table 19).

Efficacy was observed both for patients with newly diagnosed disease and for patients with relapsing disease (Table 20).

Table 19 Percentage ofadult patients who achieved complete remission at 6 months (Intent-to-treat population*)

	MabThera (n = 99)	Cyclophosphamide (n = 98)	Treatment Dif erence (MabThera- Cyclophosphamide)
Rate	63.6%	53.1%	10.6% 95.1%[b] CI (-3.2%, 24.3%) [a]

- CI = confidence interval.
- * Worst case imputation

[a] Non-inferiority was demonstrated since the lower bound (- 3.2%) was higher than the pre-determined non-inferiority margin (- 20%).

[b] The 95.1% confidence level reflects an additional 0.001 alpha to account for an interim ef icacy analysis.

Table 20 Complete remission at 6-months by disease status

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

Worst case imputation is applied for patients with missing data

Complete remission at 12 and 18 months

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

Laboratoryevaluations

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

Adult maintenance treatment

A total of 117 patients (88 with GPA, 24 with MPA, and 5 with renal-limited ANCA-associated vasculitis) in disease remission were randomized to receive azathioprine (59 patients) or MabThera (58 patients) in a prospective, multi-center, controlled, open-label study. Included patients were 21 to 75 years of age and had newly diagnosed or relapsing disease in complete remission after combined treatment with glucocorticoids and pulse cyclophosphamide. The majority of patients were ANCA-positive at diagnosis or during the course of their disease; had histologically confirmed necrotizing small-vessel vasculitis with a clinical phenotype of GPA or MPA, or renal limited ANCA-associated vasculitis; or both.

Remission-induction therapy included IV prednisone, administered as per the investigator's discretion, preceded in some patients by methylprednisolone pulses, and pulse cyclophosphamide until remission was attained after 4 to 6 months. At that time, and within a maximum of 1 month after the last cyclophosphamide pulse, patients were randomly assigned to receive either MabThera (two 500 mg IV infusions separated by two weeks (on Day 1 and Day 15) followed by 500 mg IV every 6 months for 18

months) orazathioprine (administered orally at a dose of2 mg/kg/day for 12 months, then 1.5 mg/kg/day for 6 months, and finally 1 mg/kg/day for 4 months (treatment discontinuation after these 22 months)). Prednisone treatment was tapered and then kept at a low dose (approximately 5 mg per day) for at least 18 months after randomization. Prednisone dose tapering and the decision to stop prednisone treatment after month 18 were left at the investigator's discretion.

All patients were followed until month 28 (10 or 6 months, respectively, after the last MabThera infusion or azathioprine dose). *Pneumocystis jirovecii* pneumonia prophylaxis was required for all patients with CD4+ T-lymphocyte counts less than 250 per cubic millimeter.

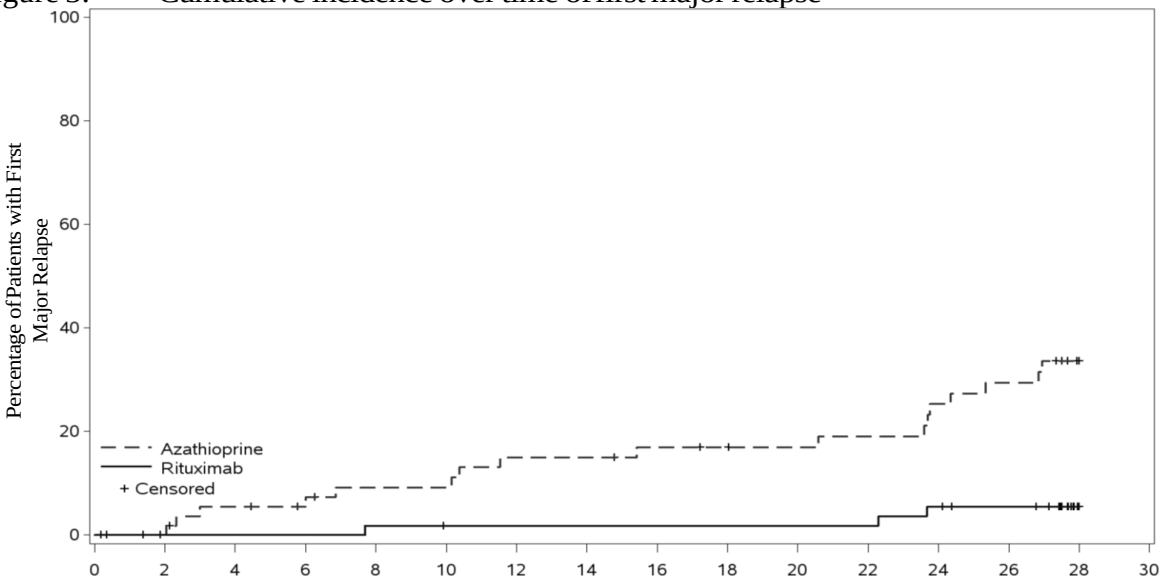
The primary outcome measure was the rate ofmajor relapse at month 28.

Results

At month 28, major relapse (defined by the reappearance ofclinical and/or laboratory signs of vasculitis activity ([BVAS] > 0) that could lead to organ failure or damage or could be life threatening) occurred in 3 patients (5%) in the MabThera group and 17 patients (29%) in the azathioprine group (p=0.0007). Minor relapses (not life threatening and not involving major organ damage) occurred in seven patients in the MabThera group (12%) and eight patients in the azathioprine group (14%).

The cumulative incidence rate curves showed that time to first major relapse was longer in patients with MabThera starting from month 2 and was maintained up to month 28 (Figure 3).

Figure 3: Cumulative incidence over time of first major relapse



Number ofSubjects with Major Relapse															
Azathioprine	0	0	3	3	5	5	8	8	9	9	9	10	13	15	17
Rituximab	0	0	0	0	1	1	1	1	1	1	1	1	3	3	3
Number ofsubjects at risk															
Azathioprine	59	56	52	50	47	47	44	44	42	41	40	39	36	34	0
Rituximab	58	56	56	56	55	54	54	54	54	54	54	54	52	50	0

Note: Patients were censored at month 28 ifthey had no event.

Laboratoryevaluations

A total of 6/34 (18%) of MabThera treated patients from the maintenance therapy clinical trial developed ADA. There was no apparent trend or negative impact ofthe presence of ADA on safety or efficacy in the maintenance therapy clinical trial.

Paediatric population

Granulomatosis with polyangiitis (GPA) andmicroscopic polyangiitis (MPA)

Study WA25615 (PePRS) was a multicenter, open-label, single-arm, uncontrolled study in 25 paediatric patients (≥ 2 to < 18 years old) with severe, active GPA or MPA. The median age of patients in the study was: 14 years (range: 6-17 years) and the majority ofpatients (20/25 [80%]) were female. A total of 19 patients (76%) had GPA and 6 patients (24%) had MPA at baseline. Eighteen patients (72%) had newly diagnosed disease upon study entry (13 patients with GPA and 5 patients with MPA) and 7 patients had relapsing disease (6 patients with GPA and 1 patient with MPA).

The study design consisted ofan initial 6-month remission induction phase, with a minimum 18-month follow-up, up to a maximum of 54 months (4.5 years) overall. Patients were to receive a minimum of3 doses ofIV methylprednisolone (30 mg/kg/day, not exceeding 1 g/day) prior to the first MabThera IV infusion. Ifclinically indicated, additional daily doses (up to three), of IV methylprednisolone could be given. The remission induction regimen consisted of four once weekly IV infusions ofMabThera at a dose of375 mg/m2 BSA, on study days 1, 8, 15 and 22 in combination with oral prednisolone or prednisone at 1 mg/kg/day (max 60 mg/day) tapered to 0.2 mg/kg/day minimum (max 10 mg/day) by Month 6. After the remission induction phase, patients could, at the discretion ofthe investigator, receive subsequent MabThera infusions on or after Month 6 to maintain PVAS remission and control disease activity (including progressive disease or flare) or to achieve first remission.

All 25 patients completed all four once weekly IV infusions for the 6-month remission induction phase. A total of24 out of25 patients completed at least 18 months offollow-up.

The objectives ofthis study were to evaluate safety, PK parameters, and e**f** icacy of MabThera in paediatric GPA and MPA patients (≥ 2 to < 18 years old). The efficacy objectives ofthe study were exploratory and principally assessed using the Pediatric Vasculitis Activity Score (PVAS) (Table 21).

Cumulative Glucocorticoid dose (IVand Oral) by Month 6:
Twenty-four out of25 patients (96%) in Study WA25615 achieved oral glucocorticoid taper to 0.2 mg/kg/day (or less than or equal to 10 mg/day, whichever was lower) at or by Month 6 during the protocol-defined oral steroid taper.

A decrease in median overall oral glucocorticoid use was observed from Week 1 (median = 45 mg prednisone equivalent dose [IQR: 35 – 60]) to Month 6 (median = 7.5 mg [IQR: 4-10]), which was subsequently maintained at Month 12 (median = 5 mg [IQR: 2-10]) and M~~m~~onth 18 (median =5 mg [IQR: 1-5]).

Follow-Up Treatment
During the Overall Study Period, patients received between 4 and 28 infusions ofMabThera (up to 4.5 yrs [53.8 months]). Patients received up to 375 mg/m^2 x 4 of MabThera, approximately every 6 months at the discretion ofthe investigator. In total, 17 out of 25 patients (68%) received additional rituximab treatment at or post Month 6 until the Common Close Out, 14 out ofthese 17 patients received additional rituximab treatment between Month 6 and Month 18.

Table 21: Study WA25615 (PePRS) - PVAS Remission at Month 1, 2, 4, 6, 12 and 18

Study visit	Number of Responders in PVAS Remission* (response rate [%]) n=25	95% CI[α]
Month 1	0	0.0%, 13.7%
Month 2	1 (4.0%)	0.1%, 20.4%
Month 4	5 (20.0%)	6.8%, 40.7%
Month 6	13 (52.0%)	31.3%, 72.2%
Month 12	18 (72.0%)	50.6%, 87.9%
Month 18	18 (72.0%)	50.6%, 87.9%

* PVAS of 0 and achieved glucocorticoid taper to 0.2 mg/kg/day (or 10 mg/day, whichever is lower) at the assessment time-point.
[α] the efficacy results are exploratory and no formal statistical testing was performed for these endpoints
MabThera, treatment (375 mg/m^2 x 4 infusions) up to Month 6 was identical for all patients. Follow-up treatment post Month 6 was at the discretion of the investigator.

Laboratory evaluations
A total of 4/25 patients (16%) developed ADA during the overall study period. Limited data shows there was no trend observed in the adverse reactions reported in ADA positive patients.

There was no apparent trend or negative impact of the presence of ADA on safety or efficacy in the paediatric GPA and MPA clinical trials.

The European Medicines Agency has waived the obligation to submit the results of studies with MabThera in paediatric population < 2 years of age in severe, active GPA or MPA. See section 4.2 for information on paediatric use.

Clinical experience in pemphigus vulgaris

PV Study 1 (Study ML22196)
The efficacy and safety of MabThera in combination with short-term, low-dose glucocorticoid (prednisone) therapy were evaluated in newly diagnosed patients with moderate to severe pemphigus (74 pemphigus vulgaris [PV] and 16 pemphigus foliaceus [PF]) in this randomised, open-label, controlled, multicenter study. Patients were between 19 and 79 years of age and had not received prior therapies for pemphigus. In the PV population, 5 (13%) patients in the MabThera group and 3 (8%) patients in the standard prednisone group had moderate disease and 33 (87%) patients in the MabThera group and 33 (92%) patients in the standard-dose prednisone group had severe disease according to disease severity defined by Harman's criteria.

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

The primary objective for the study was complete remission (complete epithelialisation and absence of new and/or established lesions) at month 24 without the use ofprednisone therapy for two months or more (CRofffor ³2 months).

PVStudy 1 Results

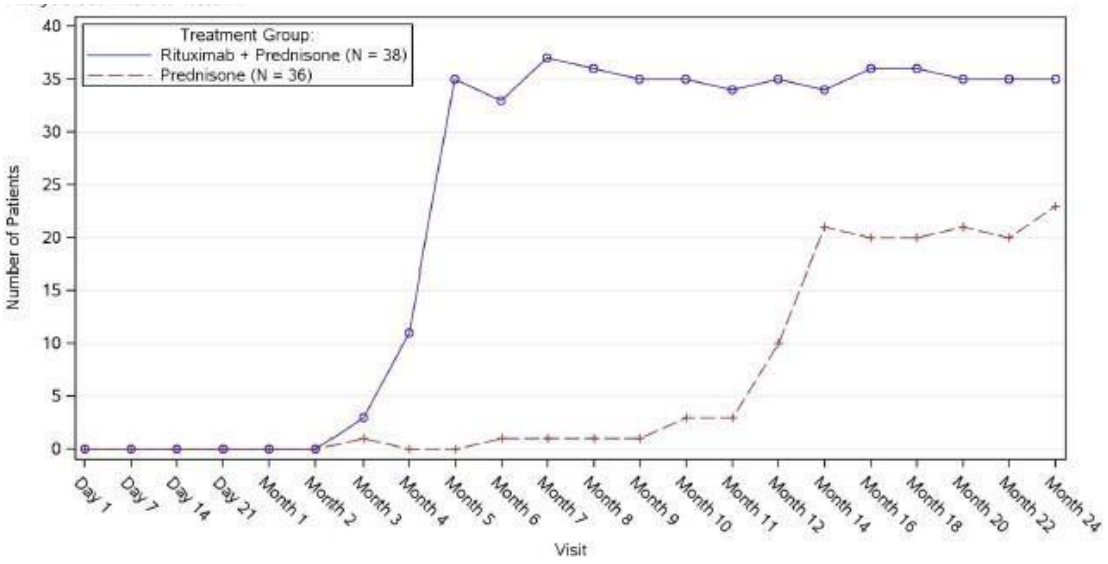
The study showed statistically significant results of MabThera and low-dose prednisone over standard-dose prednisone in achieving CRoff³ 2 months at month 24 in PV patients (see Table 22).

Table 22 Percentage of PV patients who achieved complete remission of corticosteroid therapy for two months or more at month 24 (Intent-to-Treat Population - PV)

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

The number ofrituximab plus low-dose prednisone patients off prednisone therapy or on minimal therapy (prednisone dose of 10 mg or less per day) compared to standard-dose prednisone patients over the 24-month treatment period shows a steroid-sparing effect ofMabThera (Figure 4).

Figure 4: Number ofpatients who were of or on minimal corticosteroid (≤10mg/day) therapy over time



Post-hoc retrospective laboratoryevaluation

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

PV Study 2 (Study WA29330)

In a randomized, double-blind, double-dummy, active-comparator, multicenter study, the efficacy and safety of MabThera compared with mycophenolate mofetil (MMF) were evaluated in patients with moderate-to-severe PV receiving 60-120 mg/day oral prednisone or equivalent (1.0-1.5 mg/kg/day) at study entry and tapered to reach a dose of 60 or 80 mg/day by Day 1. Patients had a confirmed

diagnosis of PV within the previous 24 months and evidence of moderate-to-severe disease (defined as a total Pemphigus Disease Area Index, PDAI, activity score of ³ 15).

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

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

PVStudy 2 Results

The study demonstrated the superiority of MabThera over MMF in combination with a tapering course oforal corticosteroids in achieving CRoff corticosteroid ³ 16 weeks at Week 52 in PV patients (Table 23).The majority ofpatients in the mITT population were newly diagnosed (74%) and 26% ofpatients had established disease (duration ofillness ³ 6 months and received prior treatment for PV).

Table 23 Percentage of PV Patients Who Achieved Sustained Complete Remission Of Corticosteroid Therapy for 16 Weeks or More at Week 52 (Modified Intent-to-Treat Population)

	MabThera (N=62)	MMF (N=63)	Difference (95% CI)	p-value
Number ofresponders (response rate [%])	25 (40.3%)	6 (9.5%)	30.80% (14.70%, 45.15%)	<0.0001
Newly diagnosed patients	19 (39.6%)	4 (9.1%)		
Patients with established disease	6 (42.9%)	2 (10.5%)		
MMF = Mycophenolate mofetil. CI = Confidence Interval. Newly diagnosed patients = duration ofillness < 6 months or no prior treatment for PV. Patients with established disease = duration ofillness ³ 6 months and received prior treatment for PV. Cochran-Mantel-Haenszel test is used for p-value.				

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

Glucocorticoidexposure

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

Disease flare

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

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

5.2 Pharmacokinetic properties

Adult Non-Hodgkin's lymphoma

Based on a population pharmacokinetic analysis in 298 NHL patients who received single or multiple infusions of MabThera as a single agent or in combination with CHOP therapy (applied MabThera doses ranged from 100 to 500 mg/m^2), the typical population estimates ofnonspecific clearance (CL_1), specific clearance (CL_2) likely contributed by B cells or tumour burden, and central compartment volume ofdistribution (V_1) were 0.14 L/day, 0.59 L/day, and 2.7 L, respectively. The estimated median terminal elimination half-life of MabThera was 22 days (range, 6.1 to 52 days). Baseline CD19-positive cell counts and size ofmeasurable tumour lesions contributed to some ofthe variability in CL_2 of MabThera in data from 161 patients given 375 mg/m^2 as an intravenous infusion for 4 weekly doses. Patients with higher CD19-positive cell counts or tumour lesions had a higher CL_2. However, a large component ofinter-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 and WHO performance status had no effect on the pharmacokinetics of MabThera. This analysis suggests that dose adjustment of MabThera with any ofthe tested covariates is not expected to result in a meaningful reduction in its pharmacokinetic variability.

MabThera, administered as an intravenous infusion at a dose of 375 mg/m^2 at weekly intervals for 4 doses to 203 patients with NHL naive to MabThera, yielded a mean C_{max} following the fourth infusion of 486 µg/mL (range, 77.5 to 996.6 µg/mL). Rituximab was detectable in the serum ofpatients 3 – 6 months after completion oflast treatment.

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

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

Paediatric DLBCL/BL/BAL/BLL

In the clinical trial studying paediatric DLBCL/BL/BAL/BLL, the PK was studied in a subset of 35 patients aged 3 years and older. The PK was comparable between the two age groups (≥3 to <12 years vs. ≥12 to <18 years). After two MabThera IV infusions of 375 mg/m^2 in each ofthe two induction cycles (cycle 1 and 2) followed by one MabThera IV infusion of 375 mg/m^2 in each ofthe consolidation cycles (cycle 3 and 4) the maximum concentration was highest after the fourth infusion (cycle 2) with a geometric mean of 347 µg/mL followed by lower geometric mean maximum concentrations thereafter (Cycle 4: 247 µg/mL). With this dose regimen, trough levels were sustained (geometric means: 41.8 µg/mL (pre-dose Cycle 2; after 1 cycle), 67.7 µg/mL (pre-dose Cycle 3, after 2 cycles) and 58.5 µg/mL (pre-dose Cycle 4, after 3 cycles)). The median elimination half-life in paediatric patients aged 3 years and older was 26 days.

The PK characteristics of MabThera in paediatric patients with DLBCL/BL/BAL/BLL were similar to what has been observed in adult NHL patients.

No PK data are available in the ≥ 6 months to < 3 years age group, however, population PK prediction supports comparable systemic exposure (AUC, Ctrough) in this age group compared to ≥ 3 years (Table 24). Smaller baseline tumor size is related to higher exposure due to lower time dependent clearance, however, systemic exposures impacted by different tumor sizes remain in the range of exposure that was efficacious and had an acceptable safety profile.

Table 24: Predicted PK Parameters following the Rituximab Dosing Regimen in Paediatric DLBCL/BL/BAL/BLL

Age group	≥ 6 mo to < 3 years	≥ 3 to < 12 years	≥ 12 to < 18 years
C_{trough} (µg/mL)	47.5 (0.01-179)	51.4 (0.00-182)	44.1 (0.00-149)
$AUC_{1\text{-}4\ cycles}$ (µg*day/mL)	13501 (278-31070)	11609 (135-31157)	11467 (110-27066)

Results are presented as median (min – max); C_{trough} is pre-dose Cycle 4.

Chronic lymphocytic leukaemia

MabThera was administered as an intravenous infusion at a first-cycle dose of 375 mg/m^2 increased to 500 mg/m^2 each cycle for 5 doses in combination with fludarabine and cyclophosphamide in CLL patients. The mean C_{max} (N=15) was 408 µg/mL (range, 97 – 764 µg/mL) after the fifth 500 mg/m^2 infusion and the mean terminal half-life was 32 days (range, 14 – 62 days).

Rheumatoid arthritis

Following two intravenous infusions of MabThera at a dose of 1000 mg, two weeks apart, the mean terminal half-life was 20.8 days (range, 8.58 to 35.9 days), mean systemic clearance was 0.23 L/day (range, 0.091 to 0.67 L/day), and mean steady-state distribution volume was 4.6 l (range, 1.7 to 7.51 L). Population pharmacokinetic analysis ofthe 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 ofdistribution and a faster clearance than female subjects. The gender- related pharmacokinetic di**f** erences are not considered to be clinically relevant and dose adjustment is not required. No pharmacokinetic data are available in patients with hepatic or renal impairment.

The pharmacokinetics ofrituximab were assessed following two intravenous (IV) doses of 500 mg and 1000 mg on Days 1 and 15 in four studies. In all these studies, rituximab pharmacokinetics were dose proportional over the limited dose range studied. Mean C_{max} for serum rituximab following first infusion ranged from 157 to 171 mg/mL for 2 x 500 mg dose and ranged from 298 to 341 mg/mL for 2 x 1000 mg dose. Following second infusion, mean C_{max} ranged from 183 to 198 mg/mL for the 2 ´ 500 mg dose and ranged from 355 to 404 mg/mL for the 2 ´ 1000 mg dose. Mean terminal elimination half-life ranged from 15 to 16 days for the 2 x 500 mg dose group and 17 to 21 days for the 2 ´ 1000 mg dose group. Mean C_{max} was 16 to 19% higher following second infusion compared to the first infusion for both doses.

The pharmacokinetics ofrituximab 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 mg/mL for 2 x 500 mg dose and 317 to 370 mg/mL for 2 x 1000 mg dose. C_{max} following second infusion, was 207 mg/mL for the 2 x 500 mg dose and ranged from 377 to 386 mg/mL for the 2 x 1000 mg dose. Mean terminal elimination half-life after the second infusion, following the second course, was 19 days for 2 x 500 mg dose and ranged from 21 to 22 days for the 2 x 1000 mg dose. PK parameters for rituximab were comparable over the two treatment courses.

The pharmacokinetic (PK) parameters in the anti-TNF inadequate responder population, following the same dosage regimen (2 x 1000 mg, IV, 2 weeks apart), were similar with a mean maximum serum concentration of 369 mg/mL and a mean terminal half-life of 19.2 days.

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

Adult Population

Based on the population pharmacokinetic analysis ofdata in 97 patients with granulomatosis with polyangiitis and microscopic polyangiitis who received 375 mg/m^2 MabThera once weekly for four doses, the estimated median terminal elimination half-life was 23 days (range, 9 to 49 days). Rituximab mean clearance and volume ofdistribution were 0.313 L/day (range, 0.116 to 0.726 L/day) and 4.50 L (range 2.25 to 7.39 L) respectively. Maximum concentration during the first 180 days (C_{max}), minimum concentration at Day 180 (C180) and Cumulative area under the curve over 180 days (AUC180) were (median [range]) 372.6 (252.3-533.5) µg/mL, 2.1 (0-29.3) µg/mL and 10302 (3653-21874)µg/mL*days, respectively. The PK parameters ofrituximab in adult GPA and MPA patients appear similar to what has been observed in rheumatoid arthritis patients.

Paediatric Population

Based on the population pharmacokinetic analysis of 25 children (6-17 years old) with GPA and MPA who received 375 mg/m^2 MabThera once weekly for four doses, the estimated median terminal elimination half-life was 22 days (range, 11 to 42 days). Rituximab mean clearance and volume of distribution were 0.221 L/day (range, 0. 0996 to 0.381 L/day) and 2.27 L (range 1.43 to 3.17 L) respectively. Maximum concentration during the first 180 days (C_{max}), minimum concentration at Day 180 (C180) and Cumulative area under the curve over 180 days (AUC180) were (median [range]) 382.8 (270.6-513.6) µg/mL, 0.9 (0-17.7) µg/mL and 9787 (4838-20446) µg/mL*day, respectively.The PK parameters ofrituximab in paediatric patients with GPA or MPA were similar to those in adults with GPA or MPA, once taking into account the BSA effect on clearance and volume ofdistribution parameters.

Pemphigus vulgaris

The PK parameters in adult PV patients receiving MabThera 1000 mg at Days 1, 15, 168, and 182 are summarized in Table 25.

Table 25 Population PK in adult PV patients from PV Study 2

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

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

5.3 Preclinical safety data

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

Developmental toxicity studies have been performed in cynomolgus monkeys at doses up to 100 mg/kg (treatment on gestation days 20-50) and have revealed no evidence oftoxicity to the foetus due to rituximab. However, dose-dependent pharmacologic depletion of B cells in the lymphoid organs ofthe 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 ofbirth 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 ofrituximab.
Specific studies to determine the e**f** ects ofrituximab 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 ofexcipients

Sodium citrate (E331)
Polysorbate 80 (E433)
Sodium chloride
Sodium hydroxide (for pH adjustment) (E524)
Hydrochloric acid (for pH adjustment) (E507)
Water for injections

6.2 Incompatibilities

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

6.3 Shelflife

Unopened vial
3 years

Diluted medicinal product

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

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

From a microbiological point ofview, the prepared infusion solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility ofthe user

and would normally not be longer than 24 hours at 2 °C – 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

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

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

6.5 Nature and contents ofcontainer

MabThera 100 mg concentrate for solution for infusion
Clear Type I glass vials with butyl rubber stopper containing 100 mg ofrituximab in 10 mL. Pack of 2 vials.

MabThera 500 mg concentrate for solution for infusion
Clear Type I glass vials with butyl rubber stopper containing 500 mg ofrituximab in 50 mL. Pack of 1 vial.

6.6 Special precautions for disposal and other handling

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

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

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

7 MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

8 MARKETING AUTHORISATION NUMBER(S)

MabThera 100 mg concentrate for solution for infusion
EU/1/98/067/001

MabThera 500 mg concentrate for solution for infusion
EU/1/98/067/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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

10 DATE OF REVISION OF THE TEXT

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

1 NAME OF THE MEDICINAL PRODUCT

MabThera 1400 mg solution for subcutaneous injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains 120 mg ofrituximab.

Each vial contains 1400 mg/11.7 mL rituximab.

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

For the full list ofexcipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

Clear to opalescent, colourless to yellowish liquid with pH of5.2 – 5.8 and osmolality of300 - 400 mOsmol/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

MabThera is indicated in adults for Non-Hodgkin's lymphoma (NHL):

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

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

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

4.2 Posology and method ofadministration

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

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

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

Posology

The recommended dose of MabThera subcutaneous formulation used for adult patients is a subcutaneous injection at a fixed dose of1400 mg irrespective ofthe patient's body surface area.

Before starting MabThera subcutaneous injections, all patients must always receive beforehand, a full dose ofMabThera by intravenous infusion, using MabThera intravenous formulation (see section 4.4).

Ifpatients were not able to receive one full MabThera intravenous infusion dose prior to the switch, they should continue the subsequent cycles with MabThera intravenous formulation until a full intravenous dose is successfully administered.
Therefore, the switch to MabThera subcutaneous formulation can only occur at the second or subsequent cycles oftreatment.

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

MabThera subcutaneous formulation is not intended for intravenous administration and should be given via subcutaneous injection only. The 1400 mg strength is intended for subcutaneous use in non Hodgkin lymphoma (NHL) only.

Follicular non-Hodgkin's lymphoma

Combination therapy
The recommended dose of MabThera in combination with chemotherapy for induction treatment of previously untreated or relapsed/ refractory patients with follicular lymphoma is: first cycle with MabThera intravenous formulation 375 mg/m^2 body surface area, followed by subsequent cycles with MabThera subcutaneous formulation injected at a fixed dose of1400 mg per cycle for up to 8cycles.

MabThera should be administered on day 1 ofeach chemotherapy cycle, after administration ofthe glucocorticoid component ofthe chemotherapy ifapplicable.

Maintenance therapy

- Previously untreated follicular lymphoma

The recommended dose of MabThera subcutaneous formulation used as a maintenance treatment for patients with previously untreated follicular lymphoma who have responded to induction treatment is: 1400 mg once every 2 months (starting 2 months after the last dose ofinduction therapy) until disease progression or for a maximum period oftwo years (12 administrations in total).

- Relapsed/refractory follicular lymphoma

The recommended dose of MabThera subcutaneous formulation used as a maintenance treatment for patients with relapsed/refractory follicular lymphoma who have responded to induction treatment is: 1400 mg once every 3 months (starting 3 months after the last dose ofinduction therapy) until disease progression or for a maximum period oftwo years (8 administrations in total).

Diffuse large B cell non-Hodgkin's lymphoma

MabThera should be used in combination with CHOP chemotherapy. The recommended dose is: first cycle, MabThera intravenous formulation: 375 mg/m^2 body surface area, followed by subsequent cycles with MabThera subcutaneous formulation injected at a fixed dose of 1400 mg per cycle. In total: 8 cycles.

MabThera is administered on day 1 ofeach chemotherapy cycle after intravenous infusion ofthe glucocorticoid component of CHOP.

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

Dose adjustments during treatment

No dose reductions of MabThera are recommended. When MabThera is given in combination with chemotherapy, standard dose reductions for the chemotherapeutic medicinal products should be applied (see section 4.8).

Special populations

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

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

Method of administration

Subcutaneous injections:
MabThera 1400 mg subcutaneous formulation should be administered as subcutaneous injection only, over approximately 5 minutes. The hypodermic injection needle must only be attached to the syringe immediately prior to administration to avoid potential needle clogging.

MabThera subcutaneous formulation should be injected subcutaneously into the abdominal wall and never into areas where the skin is red, bruised, tender, hard or areas where there are moles or scars.

No data are available on performing the injection in other sites of the body, therefore injections should be restricted to the abdominal wall.

During the treatment course with MabThera subcutaneous formulation, other medicinal products for subcutaneous administration should preferably be given at different sites.

If an injection is interrupted it can be resumed at the same site or another location may be used, if appropriate.

Intravenous infusion administration:
The Summary of Product Characteristics (SmPC) of MabThera 100 mg and 500 mg concentrate for solution for infusion should be referred to for information on dosing instructions and method of administration.

4.3 Contraindications

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

Active, severe infections (see section 4.4).

Patients in a severely immunocompromised state.

4.4 Special warnings and precautions for use

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

The information provided in the section 4.4 pertains to the use of MabThera subcutaneous formulation in the approved indications *Treatment of non-Hodgkin's lymphoma (strength 1400 mg) and Treatment of Chronic Lymphocytic Leukaemia* (strength 1600 mg). For information related to the other indications, please refer to the SmPC of MabThera intravenous formulation.

The use of MabThera subcutaneous formulation as monotherapy in patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy cannot be recommended as the safety of the once weekly subcutaneous administration has not been established.

Progressive multifocal leukoencephalopathy

Use of MabThera may be associated with an increased risk of progressive multifocal leukoencephalopathy (PML). Patients must be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML. If PML is suspected, further dosing must be suspended until PML has been excluded. The clinician should evaluate the patient to determine if the symptoms are indicative of neurological dysfunction, and if so, whether these symptoms are possibly suggestive of PML. Consultation with a neurologist should be considered as clinically indicated.

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

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

If a patient develops PML, the dosing of MabThera must be permanently discontinued.

Following reconstitution of the immune system in immunocompromised patients with PML, stabilisation or improved outcome has been seen. It remains unknown if early detection of PML and suspension of MabThera therapy may lead to similar stabilisation or improved outcome.

Infusion/Administration-related reactions

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

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

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

Severe cytokine release syndrome is characterised by severe dyspnea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. This syndrome may be associated with some features of tumour lysis syndrome such as hyperuricaemia, hyperkalaemia, hypocalcaemia, hyperphosphaetemia, acute renal failure, elevated lactate dehydrogenase (LDH) and may be associated with acute respiratory failure and death. The acute respiratory failure may be accompanied by events such as pulmonary interstitial infiltration or oedema, visible on a chest X-ray. The syndrome frequently manifests itself within one or two hours of initiating

the first infusion. Patients with a history ofpulmonary insufficiency or those with pulmonary tumour infiltration may be at greater risk ofpoor outcome and should be treated with increased caution. Patients who develop severe cytokine release syndrome should have their infusion interrupted immediately (see section 4.2) and should receive aggressive symptomatic treatment. Since initial improvement ofclinical symptoms may be followed by deterioration, these patients should be closely monitored until tumour lysis syndrome and pulmonary infiltration have been resolved or ruled out. Further treatment ofpatients after complete resolution ofsigns and symptoms has rarely resulted in repeated severe cytokine release syndrome.

Patients with a high tumour burden or with a high number ($\geq 25 \times 10^9$/L) ofcirculating malignant cells, who may be at higher risk ofespecially severe cytokine release syndrome, should be treated with extreme caution. These patients should be very closely monitored throughout the first infusion. Consideration should be given to the use ofa 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 ifthe lymphocyte count is still $>25 \times 10^9$/L.

Anaphylactic and other hypersensitivity reactions have been reported following the intravenous administration ofproteins to patients. In contrast to cytokine release syndrome, true hypersensitivity reactions typically occur within minutes after starting infusion. Medicinal products for the treatment of hypersensitivity reactions, e.g., epinephrine (adrenaline), antihistamines and glucocorticoids, should be available for immediate use in the event ofan allergic reaction during administration of MabThera. Clinical manifestations ofanaphylaxis may appear similar to clinical manifestations ofthe cytokine release syndrome (described above). Reactions attributed to hypersensitivity have been reported less frequently than those attributed to cytokine release.

Additional reactions reported in some cases were myocardial infarction, atrial fibrillation, pulmonary oedema and acute reversible thrombocytopenia.

Since hypotension may occur during MabThera administration, consideration should be given to withholding anti-hypertensive medicines 12 hours prior to giving MabThera.

Infusion related adverse reactions ofall kinds have been observed in 77% ofpatients treated with MabThera intravenous formulation (including cytokine release syndrome accompanied by hypotension and bronchospasm in 10 % ofpatients) see section 4.8. These symptoms are usually reversible with interruption of MabThera infusion and administration ofan anti-pyretic, an antihistaminic, and, occasionally, oxygen, intravenous saline or bronchodilators, and glucocorticoids if required. Please see cytokine release syndrome above for severe reactions.

Administration related reactions have been observed in up to 50% ofpatients treated with MabThera subcutaneous formulation in clinical trials. The reactions occurring within 24 hours ofthe subcutaneous injection consisted primarily oferythema pruritus, rash and injections site reactions such as pain, swelling and redness and were generally ofmild or moderate (grade 1 or 2) and transient nature (see section 4.8).

Local cutaneous reactions were very common in patients receiving MabThera subcutaneous in clinical trials. Symptoms included pain, swelling, induration, haemorrhage, erythema, pruritus and rash (see section 4.8). Some local cutaneous reactions occurred more than 24 hours after the MabThera subcutaneous administration. The majority oflocal cutaneous reactions seen following administration of MabThera subcutaneous formulation was mild or moderate and resolved without any specific treatment.

Before starting MabThera subcutaneous injections, all patients must always receive beforehand, a full dose of MabThera by intravenous infusion, using MabThera intravenous formulation. The highest risk ofexperiencing an administration related reaction is generally observed at cycle one. Beginning the

therapy with MabThera intravenous infusion would allow a better handling ofthe administration reactions by slowing or stopping the intravenous infusion.

Ifpatients were not able to receive one full MabThera intravenous infusion dose prior to the switch, they should continue the subsequent cycles with MabThera intravenous formulation until a full intravenous dose is successfully administered. Therefore, the switch to MabThera subcutaneous formulation can only occur at the second or subsequent cycles oftreatment.

As with the intravenous formulation, MabThera subcutaneous formulation should be administered in an environment where full resuscitation facilities are immediately available and under the close supervision ofan experienced healthcare professional. Premedication consisting ofan analgesic/antipyretic and an antihistamine should always be administered before each dose of MabThera subcutaneous formulation. Premedication with glucocorticoids should also be considered.

Patients should be observed for at least 15 minutes following MabThera subcutaneous administration. A longer period may be appropriate in patients with an increased risk of hypersensitivity reactions.

Patients should be instructed to contact their treating physician immediately ifsymptoms that are suggestive ofsevere hypersensitivity or cytokine release syndrome occur at any time after medicinal product administration.

Cardiac disorders

Angina pectoris, cardiac arrhythmias such as atrial flutter and fibrillation, heart failure and/or myocardial infarction have occurred in patients treated with MabThera. Therefore patients with a history ofcardiac disease and/or cardiotoxic chemotherapy should be monitored closely.

Haematological toxicities

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

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

Infections

Serious infections, including fatalities, can occur during therapy with MabThera (see section 4.8). MabThera should not be administered to patients with an active, severe infection (e.g. tuberculosis, sepsis and opportunistic infections, see section 4.3).

Physicians should exercise caution when considering the use of MabThera in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection (see section 4.8).

Cases ofhepatitis B reactivation have been reported in patients receiving the MabThera intravenous formulation including fulminant hepatitis with fatal outcome. The majority ofthese patients were also exposed to cytotoxic chemotherapy. Hepatitis B virus (HBV) screening should be performed in all patients before initiation oftreatment with MabThera. At minimum this should include HBsAg-status and HBcAb-status. These can be complemented with other appropriate markers as per local guidelines. Patients with active hepatitis B disease should not be treated with MabThera. Patients with positive hepatitis B serology (either HBsAg or HBcAb) should consult liver disease experts before

start oftreatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation.

Very rare cases of PML have been reported during post-marketing use ofthe MabThera intravenous formulation in NHL (see section 4.8). The majority ofpatients had received rituximab in combination with chemotherapy or as part ofa hematopoietic stem cell transplant.

Immunisation

The safety ofimmunisation with live viral vaccines, following MabThera therapy has not been studied for NHL patients and vaccination with live virus vaccines is not recommended. Patients treated with MabThera may receive non-live vaccinations; however, with non-live vaccines response rates may be reduced. In a non-randomized study, patients with relapsed low-grade NHL who received the MabThera intravenous formulation as monotherapy when compared to healthy untreated controls had a lower rate ofresponse to vaccination with tetanus recall antigen (16% vs. 81%) and Keyhole Limpet Haemocyanin (KLH) neoantigen (4% vs. 69% when assessed for >2-fold increase in antibody titer).

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

Skin reactions

Severe skin reactions such as Toxic Epidermal Necrolysis (Lyell's Syndrome) and Stevens - Johnson syndrome, some with fatal outcome, have been reported (see section 4.8). In case ofsuch an event, with suspected relationship to MabThera, treatment should be permanently discontinued.

4.5 Interaction with other medicinal products and other forms ofinteraction

Currently, there are limited data on possible drug interactions with MabThera.

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

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

4.6 Fertility, pregnancy and lactation

Contraception in males and females

Due to the long retention time ofrituximab in B cell depleted patients, women ofchildbearing potential must employ effective contraceptive methods during and for 12 months after treatment with MabThera.

Pregnancy

IgG immunoglobulins are known to cross the placental barrier.

B-cell levels in human neonates following maternal exposure to MabThera have not been studied in clinical trials. There are no adequate and well-controlled data from studies in pregnant women, however transient B-cell depletion and lymphocytopenia have been reported in some infants born to mothers exposed to MabThera during pregnancy. Similar effects have been observed in animal studies

(see section 5.3).For these reasons MabThera should not be administered to pregnant women unless the possible benefit outweighs the potential risk.

Breast-feeding

Limited data on rituximab excretion into breast milk suggest very low milk levels (relative infant dose less than 0.4%). Few cases of follow-up ofbreastfed infants describe normal growth and development up to 1.5 years. However, as these data are limited and the long-term outcomes of breastfed infants remain unknown, breastfeeding is not recommended while being treated with rituximab and optimally for 12 months following rituximab treatment.

Fertility

Animal studies did not reveal deleterious effects ofrituximab or recombinant human hyaluronidase (rHuPH20) on reproductive organs.

4.7 Effects on ability to drive and use machines

No studies on the effects of MabThera on the ability to drive and use machines have been performed, although the pharmacological activity and adverse reactions reported to date suggest that MabThera would have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The information provided in this section pertains to the use ofMabThera in oncology.
For information related to the autoimmune indications, please refer to the SmPC of MabThera intravenous formulation.

Summary ofthe safety profile

During the development programme, the safety profile of MabThera subcutaneous formulation was comparable to that ofthe intravenous formulation with the exception oflocal cutaneous reactions. Local cutaneous reactions, including injection site reactions were very common in patients receiving MabThera subcutaneous formulation. In the phase 3 SABRINA trial (BO22334), local cutaneous reaction were reported in up to 20% ofpatients receiving subcutaneous MabThera. The most common local cutaneous reactions in the Mabthera subcutaneous arm were injection erythema (13%), injection pain (7%) and injection site oedema (4%).Events seen following subcutaneous administration were mild or moderate, apart from one patient who reported a local cutaneous reaction of Grade 3 intensity (injection site rash) following the first MabThera subcutaneous administration (Cycle 2). Local cutaneous reactions ofany grade in the MabThera subcutaneous arm were most common during the first subcutaneous cycle (Cycle 2), followed by the second, and the incidence decreased with subsequent injections.

Adverse reactions reported in MabThera subcutaneous formulation usage

The risk ofacute administration-related reactions associated with the subcutaneous formulation of MabThera was assessed in two open-label trials involving patients with follicular lymphoma during induction and maintenance (SABRINA/BO22334) and during maintenance only (SparkThera/BP22333). InSABRINA, severe administration-related reactions (grade≥3) were reported in two patients (2%) following administration of MabThera subcutaneous formulation. These events were Grade 3 injection site rash and dry mouth. InSparkThera, no severe administration-related reactions were reported.

Adverse reactions reported in MabThera intravenous formulation usage

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

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

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

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

The most frequent reported or observed serious adverse reactions were:

- Infusion-related reactions (including cytokine-release syndrome, tumour-lysis syndrome), seesection 4.4.
- Infections, see section 4.4.
- Cardiovascular disorders, see section 4.4.

Other serious ADRs reported include hepatitis B reactivation and PML (see section 4.4.).

The frequencies of ADRs reported with MabThera alone or in combination with chemotherapy are summarised in Table 1. Frequencies are defined as very common (³ 1/10), common (³ 1/100 to < 1/10), uncommon (³ 1/1,000 to < 1/100), rare (³ 1/10,000 to < 1/1000), very rare (< 1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order ofdecreasing seriousness.

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

Tabulated list ofadverse reactions

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

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

MedDRA System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not known
Immune system disorders	infusion related reactions[4], angioedema	hypersensitivity		anaphylaxis	tumour lysis syndrome, cytokine release syndrome[4], serum sickness	infusion-related acute reversible thrombocytopenia [4]
Metabolism and nutrition disorders		hyperglycaemia, weight decrease, peripheral oedema, face oedema, increased LDH, hypocalcaemia				
Psychiatric disorders			depression, nervousness,			
Nervous system disorders		paraesthesia, hypoaesthesia, agitation, insomnia, vasodilatation, dizziness, anxiety	dysgeusia		peripheral neuropathy, facial nerve palsy[5]	cranial neuropathy, loss ofother senses[5]
Eye disorders		lacrimation disorder, conjunctivitis			severe vision loss[5]	
Ear and labyrinth disorders		tinnitus, ear pain				hearing loss[5]
Cardiac disorders		[+]myocardial infarction[4 and 6], arrhythmia, [+]atrial fibrillation, tachycardia, [+]cardiac disorder	[+]left ventricular failure, [+]supraventricular tachycardia, [+]ventricular tachycardia, [+]angina, [+]myocardial ischaemia, bradycardia	severe cardiac disorders [4 and 6]	heart failure[4 and 6]	
Vascular disorders		hypertension, orthostatic hypotension, hypotension			vasculitis (predominately cutaneous), leukocytoclastic vasculitis	
Respiratory, thoracic and mediastinal disorders		Bronchospasm[4], respiratory disease, chest pain, dyspnoea, increased cough, rhinitis	asthma, bronchiolitis obliterans, lung disorder, hypoxia	interstitial lung disease[7]	respiratory failure[4],	lung infiltration,
Gastrointestinal disorders	nausea	vomiting, diarrhoea, abdominal pain, dysphagia, stomatitis, constipation, dyspepsia, anorexia, throat irritation	abdominal enlargement		gastro-intestinal perforation[7]	

MedDRA System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not known
Skin and subcutaneous tissue disorders	pruritis, rash, +alopecia	urticaria, sweating, night sweats, +skin disorder			severe bullous skin reactions, Stevens-Johnson Syndrome, toxic epidermal necrolysis (Lyell's Syndrome)[7]	
Musculoskeletal, connective tissue disorders		hypertonia, myalgia, arthralgia, back pain, neck pain, pain				
Renal and urinary disorders					renal failure[4]	
General disorders and administration site conditions	fever , chills, asthenia, headache	tumour pain, flushing, malaise, cold syndrome, +fatigue, +shivering, +multi-organ failure[4]	infusion site pain			
Investigations	decreased IgG levels					

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

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

[2] see also section infection below

[3] see also section haematologic adverse reactions below

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

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

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

[7] includes fatal cases

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

Signs and symptoms suggestive ofan infusion-related reaction were reported in more than 50 % of patients in clinical trials involving MabThera intravenous formulation, and were predominantly seen during the first infusion, usually in the first one to two hours. These symptoms mainly comprised fever, chills and rigors. Other symptoms included flushing, angioedema, bronchospasm, vomiting, nausea, urticaria/rash, fatigue, headache, throat irritation, rhinitis, pruritus, pain, tachycardia, hypertension, hypotension, dyspnoea, dyspepsia, asthenia and features oftumour lysis syndrome. Severe infusion-related reactions (such as bronchospasm, hypotension) occurred in up to 12 % ofthe cases. Additional reactions reported in some cases were myocardial infarction, atrial fibrillation, pulmonary oedema and acute reversible thrombocytopenia. Exacerbations ofpre-existing cardiac conditions such as angina pectoris or congestive heart failure or severe cardiac disorders (heart failure, myocardial infarction, atrial fibrillation), pulmonary oedema, multi-organ failure, tumour lysis syndrome, cytokine release syndrome, renal failure, and respiratory failure were reported at lower or unknown frequencies. The incidence ofinfusion-related symptoms decreased substantially with subsequent intravenous infusions and is <1% ofpatients by the eighth cycle of MabThera (containing) treatment.

Description ofselected adverse reactions

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

Localized candida infections as well as Herpes zoster were reported at a higher incidence in the MabThera-containing arm ofrandomized studies. Severe infections were reported in about 4% of patients treated with MabThera monotherapy. Higher frequencies ofinfections overall, including grade 3 or 4 infections, were observed during MabThera maintenance treatment up to 2 years when compared to observation. There was no cumulative toxicity in terms ofinfections reported over a 2-year treatment period. In addition, other serious viral infections either new, reactivated or exacerbated, some ofwhich were fatal, have been reported with MabThera treatment. The majority of patients had received MabThera in combination with chemotherapy or as part ofa hematopoietic stem cell transplant. Examples ofthese serious viral infections are infections caused by the herpes viruses (Cytomegalovirus, Varicella Zoster Virus and Herpes Simplex Virus), JC virus (PML) and hepatitis C virus. Cases of fatal PML that occurred after disease progression and retreatment have also been reported in clinical trials. Cases ofhepatitis B reactivation, have been reported, the majority ofwhich were in patients receiving MabThera in combination with cytotoxic chemotherapy. Progression of Kaposi's sarcoma has been observed in MabThera-exposed patients with pre-existing Kaposi's sarcoma. These cases occurred in non-approved indications and the majority ofpatients were HIV positive.

Haematologic adverse reactions
In clinical trials with MabThera monotherapy given for 4 weeks, haematological abnormalities occurred in a minority ofpatients and were usually mild and reversible. Severe (grade 3/4) neutropenia was reported in 4.2%, anaemia in 1.1% and thrombocytopenia in 1.7% ofthe patients. During MabThera maintenance treatment for up to 2 years, leucopoenia (5% vs. 2%, grade 3/4) and neutropenia (10% vs. 4%, grade 3/4) were reported at a higher incidence when compared to observation. The incidence ofthrombocytopenia was low (<1 %, grade 3/4) and was not different between treatment arms. During the treatment course in studies with MabThera in combination with chemotherapy, grade 3/4 leucopoenia (R-CHOP 88% vs. CHOP 79%), neutropenia (R-CVP 24% vs. CVP 14%; R-CHOP 97% vs. CHOP 88%), were usually reported with higher frequencies when compared to chemotherapy alone. However, the higher incidence ofneutropenia in patients treated with MabThera and chemotherapy was not associated with a higher incidence ofinfections and infestations compared to patients treated with chemotherapy alone. There were no differences reported for the incidence ofanaemia. Some cases oflate neutropenia occurring more than four weeks after the last infusion of MabThera were reported.

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

Cardiovascular adverse reactions
Cardiovascular reactions during clinical trials with MabThera monotherapy were reported in 18.8% of patients with the most frequently reported events being hypotension and hypertension. Cases ofgrade 3 or 4 arrhythmia (including ventricular and supraventricular tachycardia) and angina pectoris during infusion were reported. During maintenance treatment, the incidence ofgrade 3/4 cardiac disorders was comparable between patients treated with MabThera and observation. Cardiac events were reported as serious adverse events (including atrial fibrillation, myocardial infarction, left ventricular failure, myocardial ischemia) in 3% ofpatients treated with MabThera compared to <1% on observation. In studies evaluating MabThera in combination with chemotherapy, the incidence of grade 3 and 4 cardiac arrhythmias, predominantly supraventricular arrhythmias such as tachycardia and atrial flutter/fibrillation, was higher in the R-CHOP group (14 patients, 6.9%) as compared to the CHOP group (3 patients, 1.5%). All ofthese arrhythmias either occurred in the context ofa MabThera infusion or were associated with predisposing conditions such as fever, infection, acute myocardial

infarction or pre-existing respiratory and cardiovascular disease. No difference between the R-CHOP and CHOP group was observed in the incidence ofother grade 3 and 4 cardiac events including heart failure, myocardial disease and manifestations ofcoronary artery disease.

Respiratorysystem
Cases ofinterstitial lung disease, some with fatal outcome have been reported.

Neurologic disorders
During the treatment period (induction treatment phase comprising of R-CHOP for at most eight cycles), four patients (2 %) treated with R-CHOP, all with cardiovascular risk factors, experienced thromboembolic cerebrovascular accidents during the first treatment cycle. There was no di**f** erence between the treatment groups in the incidence ofother thromboembolic events. In contrast, three patients (1.5%) had cerebrovascular events in the CHOP group, all ofwhich occurred during the follow-up period.

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

Gastrointestinal disorders
Gastrointestinal perforation in some cases leading to death has been observed in patients receiving MabThera for treatment of Non-Hodgkin's lymphoma (NHL). In the majority ofthese cases, MabThera was administered with chemotherapy.

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

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

Patient subpopulations - MabThera monotherapy
Elderly (³ 65 years):
The incidence of ADRs ofall grades and grade 3 /4 ADR was similar in elderly patients compared to younger patients (<65 years).

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

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

Reporting ofsuspected adverse reactions

Reporting suspected adverse reactions after authorisation ofthe medicinal product is important. It allows continued monitoring ofthe benefit/risk balance ofthe medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Limited experience with doses higher than the approved dose ofintravenous MabThera formulation is available from clinical trials in humans. The highest intravenous dose of MabThera tested in humans to date is 5000 mg (2250 mg/m^2), tested in a dose escalation study in patients with CLL. No additional safety signals were identified.
Patients who experience overdose should have immediate interruption oftheir infusion and be closely monitored.

Three patients in the MabThera subcutaneous formulation trial SABRINA (BO22334) were inadvertently administered subcutaneous formulation through the intravenous route up to a maximum rituximab dose of 2780 mg with no untoward e**f** ect.
Patients who experience overdose or medication error should be closely monitored.

In the post-marketing setting five cases of MabThera overdose have been reported. Three cases had no reported adverse event. The two adverse events that were reported were flu-like symptoms, with a dose of1.8 g ofrituximab and fatal respiratory failure, with a dose of 2 g ofrituximab.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

MabThera subcutaneous formulation contains recombinant human hyaluronidase (rHuPH20), an enzyme used to increase the dispersion and absorption ofco-administered substances when administered subcutaneously.

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

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

The Fab domain ofrituximab binds to the CD20 antigen on B lymphocytes and the Fc domain can recruit immune effector functions to mediate B cell lysis. Possible mechanisms ofeffector-mediated cell lysis include complement-dependent cytotoxicity (CDC) resulting from C1q binding, and antibody-dependent cellular cytotoxicity (ADCC) mediated by one or more ofthe Fc**g** receptors on the surface ofgranulocytes, macrophages and NK cells. Rituximab binding to CD 20 antigen on B lymphocytes has also been demonstrated to induce cell death via apoptosis.

Peripheral B cell counts declined below normal following completion ofthe first dose of MabThera. In patients treated for hematological malignancies, B cell recovery began within 6 months oftreatment and generally returned to normal levels within 12 months after completion oftherapy, although in some patients this may take longer (up to a median recovery time of 23 months post-induction therapy). In rheumatoid arthritis patients, immediate depletion ofB cells in the peripheral blood was

observed following two infusions of 1000 mg MabThera separated by a 14 day interval. Peripheral blood B cell counts begin to increase from week 24 and evidence for repopulation is observed in the majority ofpatients by week 40, whether MabThera was administered as monotherapy or in combination with methotrexate.

Clinical experience ofMabThera subcutaneous formulation in Non-Hodgkin's lymphoma

The clinical experience of MabThera subcutaneous formulation in Non-Hodgkin's lymphoma is based on data from a phase III clinical trial (SABRINA BO22334) in patients with follicular lymphoma (FL) and a phase Ib dose-finding/dose-confirmation trial (SparkThera BP22333) in patients with FL. Results from trial BP22333 are presented in section 5.2.

Trial BO22334 (SABRINA)

A two-stage phase III, international, multi-centre, randomised, controlled, open-label trial was conducted in patients with previously untreated follicular lymphoma, to investigate the non-inferiority ofthe pharmacokinetic profile, together with e**f** icacy and safety of MabThera subcutaneous formulation in combination with CHOP or CVP versus MabThera intravenous formulation in combination with CHOP or CVP.

The objective ofthe first stage was to establish the rituximab subcutaneous dose that resulted in comparable MabThera subcutaneous formulation serum C_{trough} levels compared with MabThera intravenous formulation, when given as part ofinduction treatment every 3 weeks (see section 5.2). Stage 1 enrolled previously untreated patients (n=127) CD20-positive, Follicular Lymphoma (FL) Grade 1, 2 or 3a.

The objective ofstage 2 was to provide additional e**f** icacy and safety data for subcutaneous rituximab compared with rituximab intravenous using the 1400 mg subcutaneous dose established in stage 1. Previously untreated patients with CD20-positive, Follicular Lymphoma Grade 1, 2 or 3a (n=283) were enrolled in the stage 2.

The overall trial design was identical among both stages and patients were randomized into the following two treatment groups:

- MabThera subcutaneous formulation (n= 205): first cycle MabThera intravenous formulationplus 7 cycles of MabThera subcutaneous formulation in combination with up to 8 cycles of CHOP or CVP chemotherapy administered every 3 weeks.

MabThera intravenous formulation was used at the standard dose of 375 mg/m^2 body surfacearea.
MabThera subcutaneous formulation was given at a fixed dose of1400 mg.
Patients achieving at least partial response (PR) were entered on the MabThera subcutaneousformulation maintenance therapy once every 8 weeks for 24 months.

- MabThera intravenous formulation (n= 205): 8 cycles of MabThera intravenous formulation in combination with up to 8 cycles of CHOP or CVP chemotherapy administered every 3 weeks. MabThera intravenous formulation was used at the standard dose of375 mg/m^2.
  Patients achieving at least PR were entered on MabThera intravenous formulation maintenance therapy once every 8 weeks for 24 months.

Key e**f** icacy results for the pooled analysis of 410 patients in SABRINA stages 1 and 2 are shown in table 2.

Table 2 Efficacy results for SABRINA (BO22334) (Intent to Treat Population)

		Pooled Stages 1 & 2 N = 410	
		Rituximab intravenous formulation (n = 205)	Rituximab subcutaneous formulation (n = 205)
ORR[a]	Point estimate	84.9% (n = 174)	84.4% (n = 173)
	95% CI	[79.2%, 89.5%]	[78.7%, 89.1%]
CRR	Point estimate	31.7% (n = 65)	32.2% (n = 66)
	95% CI	[25.4%, 38.6%]	[25.9%, 39.1%]
PFS[b]	Proportion with PFS event	34.6% (n = 71)	31.7% (n = 65)
	Hazard ratio (95% CI)	0.90 [0.64%, 1.26%]	

ORR – Overall Response Rate
CRR – Complete Response Rate
PFS – Progression-Free Survival (proportion with event, disease progression/relapse or death from any cause)
[a] – at end ofInduction
[b] – at time offinal analysis (median follow-up 58 months)

Exploratory analyses showed response rates among BSA, chemotherapy and gender subgroups were not notably different from the ITT population.

Immunogenicity

Data from the development programme of MabThera subcutaneous formulation indicate that the formation ofanti-rituximab antibodies after subcutaneous administration is comparable with that observed after intravenous administration. In the SABRINA trial (BO22334) the incidence of treatment-induced/enhanced anti-rituximab antibodies was low and similar in the intravenous and subcutaneous groups (1.9% vs. 2%, respectively). The incidence oftreatment-induced/enhanced anti-rHuPH20 antibodies was 8% in the intravenous group compared with 15% in the subcutaneous group, and none ofthe patients who tested positive for anti-rHuPH20 antibodies tested positive for neutralizing antibodies.

The overall proportion ofpatients found to have anti-rHuPH20 antibodies remained generally constant over the follow-up period in both cohorts. The clinical relevance ofthe development ofanti-rituximab antibodies or anti-rHuPH20 antibodies after treatment with MabThera subcutaneous formulation is not known.
There was no apparent impact ofthe presence ofanti-rituximab or anti-rHuPH20 antibodies on safety or efficacy.

Clinical experience ofMabThera concentrate for solution for infusion in Non-Hodgkin's lymphoma

Follicular lymphoma

Initial treatment in combination with chemotherapy

In an open-label randomised trial, a total of 322 previously untreated patients with follicular lymphoma were randomised to receive either CVP chemotherapy (cyclophosphamide 750 mg/m^2, vincristine 1.4 mg/m^2 up to a maximum of 2 mg on day 1, and prednisolone 40 mg/m^2/day on days 1 -5) every 3 weeks for 8 cycles or MabThera 375 mg/m^2 in combination with CVP (R-CVP). MabThera was administered on the first day ofeach treatment cycle. A total of321 patients (162 R-CVP, 159 CVP) received therapy and were analysed for efficacy. The median follow up ofpatients 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 ofpatients 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 ofresponse was 37.7 months in the R-CVP group and was 13.5 months in the CVP group ($p < 0.0001$, log-rank test).

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

Results from three other randomized trials using MabThera in combination with chemotherapy regimen other than CVP (CHOP, MCP, CHVP/Interferon-α) have also demonstrated significant improvements in response rates, time-dependent parameters as well as in overall survival. Key results from all four trials are summarized in table 3.

Table 3 Summary of key results from four phase III randomized trials evaluating the benefit of MabThera with different chemotherapy regimens in follicular lymphoma

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

EFS – Event Free Survival
TTP – Time to progression or death
PFS – Progression-Free Survival
TTF – Time to Treatment Failure
OS rates – survival rates at the time ofthe analyses

Maintenance therapy

Previously untreated follicular lymphoma

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

The pre-specified primary analysis was conducted at a median observation time of 25 months from randomization, maintenance therapy with MabThera resulted in a clinically relevant and statistically significant improvement in the primary endpoint ofinvestigator assessed progression-free survival (PFS) as compared to observation in patients with previously untreated follicular lymphoma (Table 4).

Significant benefit from maintenance treatment with MabThera was also seen for the secondary endpoints event-free survival (EFS), time to next anti-lymphoma treatment (TNLT) time to next chemotherapy (TNCT) and overall response rate (ORR) in the primary analysis (Table 4).

Data from extended follow-up ofpatients in the study (median follow-up 9 years) confirmed the long-term benefit ofMabThera maintenance therapy in terms ofPFS, EFS, TNLT and TNCT (Table 4).

Table 4 Overview of efficacy results for MabThera maintenance vs. observation at the protocol-defined primary analysis and after 9 years median follow-up (final analysis)

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

* at end ofmaintenance/observation; final analysis results based on median follow-up of73 months.
FU: follow-up; NR: not reached at time ofclinical cut off, TNCT: time to next chemotherapy treatment; TNLT: time to next anti lymphoma treatment.

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

Relapsed/Refractory follicular lymphoma

In a prospective, open label, international, multi-centre, phase III trial, 465 patients with relapsed/refractory follicular lymphoma were randomised in a first step to induction therapy with either CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone; n=231) or MabThera plus CHOP (R-CHOP, n=234). The two treatment groups were well balanced with regard to baseline characteristics and disease status. A total of 334 patients achieving a complete or partial remission following induction therapy were randomised in a second step to MabThera maintenance therapy (n=167) or observation (n=167). MabThera maintenance treatment consisted ofa single infusion of MabThera at 375 mg/m^2 body surface area given every 3 months until disease progression or for a maximum period oftwo years.

The final efficacy analysis included all patients randomized to both parts of the trial. After a median observation time of 31 months for patients randomised to the induction phase, R-CHOP significantly improved the outcome of patients with relapsed/refractory follicular lymphoma when compared to CHOP (see Table 5).

Table 5 Induction phase: overview of efficacy results for CHOP vs. R-CHOP (31 months median observation time)

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

[1)] Estimates were calculated by hazard ratios

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

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

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

Table 6 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 ofinduction regimen (CHOP or R-CHOP) or quality ofresponse to induction treatment (CR or PR) (table 6). MabThera maintenance treatment significantly prolonged median PFS in patients responding to CHOP induction therapy (median PFS 37.5 months vs. 11.6 months, p< 0.0001) as well as in those responding to R-CHOP induction (median PFS 51.9 months vs. 22.1 months, p=0.0071). Although subgroups were small, MabThera maintenance treatment provided a significant benefit in terms of overall survival for both patients responding to CHOP and patients responding to R-CHOP, although longer follow-up is required to confirm this observation.

Diffuse large B cell non-Hodgkin's lymphoma

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

The final efficacy analysis included all randomised patients (197 CHOP, 202 R-CHOP), and had a median follow-up duration ofapproximately 31 months. The two treatment groups were well balanced in baseline disease characteristics and disease status. The final analysis confirmed that R-CHOP treatment was associated with a clinically relevant and statistically significant improvement in the duration ofevent-free survival (the primary efficacy parameter; where events were death, relapse or progression oflymphoma, or institution ofa new anti-lymphoma treatment) (p = 0.0001). Kaplan Meier estimates ofthe median duration ofevent-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 ofthe duration ofoverall survival, carried out with a median follow-up duration

of 60 months, confirmed the benefit of R-CHOP over CHOP treatment (p=0.0071), representing a risk reduction of 32 %.

The analysis of all secondary parameters (response rates, progression-free survival, disease-free survival, duration of response) verified the treatment effect of R-CHOP compared to CHOP. The complete response rate after cycle 8 was 76.2 % in the R-CHOP group and 62.4 % in the CHOP group (p=0.0028). The risk of disease progression was reduced by 46 % and the risk of relapse by 51 %. In all patients subgroups (gender, age, age adjusted IPI, Ann Arbor stage, ECOG, β2 microglobulin, LDH, albumin, B symptoms, bulky disease, extranodal sites, bone marrow involvement), the risk ratios for event-free survival and overall survival (R-CHOP compared with CHOP) were less than 0.83 and 0.95 respectively. R-CHOP was associated with improvements in outcome for both high- and low-risk patients according to age adjusted IPI.

Clinical laboratory findings

Of 67 patients evaluated for HAMA, no responses were noted. Of 356 patients evaluated for ADA, 1.1 % (4 patients) were positive.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with rituximab in all subsets of the paediatric population with follicular lymphoma. See Section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Absorption

Rituximab pharmacokinetics following single dose administration of MabThera subcutaneous 375 mg/m^2, 625 mg/ m^2 and 800 mg/ m^2 were compared with MabThera intravenous 375 mg/ m^2 in FL patients. Following subcutaneous administration, the absorption of rituximab is slow, reaching maximal concentrations about 3 days after administration. Based on popPK analysis an absolute bioavailability of 71% was estimated. Rituximab exposure increased dose proportional over the 375 mg/m^2 to 800 mg/m^2 subcutaneous dose range. Pharmacokinetic parameters such as clearance, distribution volume, and elimination half-life were comparable for both formulations.

Trial BP22333 (SparkThera)

A two-stage phase Ib trial to investigate the pharmacokinetics, safety and tolerability of MabThera subcutaneous formulation in patients with follicular lymphoma (FL) as part of maintenance treatment. In stage 2, MabThera subcutaneous formulation at a fixed dose of 1400 mg was administered as subcutaneous injection during maintenance treatment, after at least one cycle of MabThera intravenous formulation to FL patients who had previously responded to MabThera intravenous formulation in induction.

The comparison of predicted median C_{max} data for MabThera subcutaneous formulation and intravenous formulation are summarized in Table 7.

Table 7: Trial BP22333 (SparkThera): Absorption - Pharmacokinetic parameters of MabTheraSC compared to MabThera IV

	MabThera subcutaneous	MabThera intravenous
Predicted median C_{max} (q2m) µg/mL	201	209
Predicted median C_{max} (q3m) µg/mL	189	184

The median T_{max} in the MabThera subcutaneous formulation was approximately 3 days as compared to the T_{max} occuring at or close to the end ofthe infusion for the intravenous formulation.

Trial BO22334 (SABRINA)

MabThera subcutaneous formulation at a fixed dose of 1400 mg was administered for 6 cycles subcutaneously during induction at 3-weekly intervals, following the first cycle ofMabThera intravenous formulation, in previously untreated FL patients in combination with chemotherapy. The serum rituximab C_{max} at cycle 7 was similar between the two treatment arms, with geometric mean (CV%) values of 250.63 (19.01) µg/mL and 236.82 (29.41) µg/mL for the intravenous and the subcutaneous formulations respectively, with the resulting geometric mean ratio ($C_{max, SC}/C_{max, IV}$) of 0.941 (90% CI: 0.872, 1.015).

Distribution/Elimination

Geometric mean C_{trough} and geometric mean AUCτ from the BP22333 and BO22334 trials are summarized in Table 8.

Table 8: Distribution/Elimination - Pharmacokinetic parameters of MabThera subcutaneous compared to MabThera intravenous

Trial BP22333 (SparkThera)				
	Geometric mean C_{trough} (q2m) µg/mL	Geometric mean C_{trough} (q3m) µg/mL	Geometric mean AUCτ cycle 2 (q2m) µg.day/mL	Geometric mean AUCτ cycle 2 (q3m) µg.day/mL
MabThera subcutaneous formulation	32.2	12.1	5430	5320
MabThera intravenous formulation	25.9	10.9	4012	3947
Trial BO22334 (SABRINA)				
	Geometric mean C_{trough} values at pre-dose cycle 8 µg/mL		Geometric mean AUC values at cycle 7 µg.day/mL	
MabThera subcutaneous formulation	134.6		3778	
MabThera intravenous formulation	83.1		2734	

In a population pharmacokinetic analysis in 403 follicular lymphoma patients who received subcutaneous and/or intravenous MabThera, single or multiple infusions ofMabThera as a single agent or in combination with chemotherapy, the population estimates ofnonspecific clearance (CL_1), initial specific clearance (CL_2) likely contributed by B cells or tumour burden, and central compartment volume ofdistribution (V_1) were 0.194 L/day, 0.535 L/day, and 4.37 L/day, respectively. The estimated median terminal elimination half-life ofMabThera subcutaneous formulation was 29.7 days (range, 9.9 to 91.2 days).The analysis data set contained 6003 quantifiable samples from 403 patients administered SC and/or IV rituximab in trials BP22333 (3736 samples from 277 patients) and BO22334 (2267 samples from126 patients). Twenty nine (0.48%) post-dose observations (all from trial BP22333) were below the quantification limit. There were no missing covariate values except baseline B-cell count. Baseline tumour load was available only in trial BO22334.

Special populations

In clinical trial BO22334, an effect was observed between body size and exposure ratios reported in cycle 7, between rituximab subcutaneous formulation 1400 mg q3w and rituximab intravenous formulation 375 mg/m2 q3w with C_{trough} ratios of 2.29, 1.31, and 1.41 in patients with low, medium and high BSA, respectively (low BSA £ 1.70 m^2; 1.70 m^2 < medium BSA < 1.90 m^2; high BSA ³ 1.90 m^2). The corresponding AUCτ ratios were 1.66, 1.17 and 1.32.

There was no evidence ofclinically relevant dependencies ofrituximab pharmacokinetics on age and sex.

Anti-rituximab antibodies were detected in only 13 patients and did not result in any clinically relevant increase in steady-state clearance.

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 oftoxicity to the foetus due to rituximab. However, dose-dependent pharmacologic depletion of B cells in the lymphoid organs ofthe 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 ofbirth and did not compromise the reaction to immunization.

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 ofrituximab.
Specific studies to determine the e**f** ects ofrituximab or rHuPH20 on fertility have not been performed. In general toxicity studies in cynomolgus monkeys no deleterious e**f** ects on reproductive organs in males or females were observed. Additionally, no effects on semen quality were shown for rHuPH20.

In embryofetal developmental studies in mice, rHuPH20 caused reduced fetal weight and loss of implantations at systemic exposures su**f** iciently in excess ofhuman therapeutic exposure.
There is no evidence ofdysmorphogenesis (i.e. teratogenesis) resulting from systemic exposure to rHuPH20.

6 PHARMACEUTICAL PARTICULARS

6.1 List ofexcipients

Recombinant human hyaluronidase (rHuPH20)
L-histidine
L-histidine hydrochloride monohydrate
a,a-trehalose dihydrate
L-methionine
Polysorbate 80 (E433)
Water for injections

6.2 Incompatibilities

No incompatibilities between MabThera subcutaneous formulation and polypropylene or polycarbonate syringe material or stainless steel transfer and injection needles and polyethylene Luer cone stoppers have been observed.

6.3 Shelflife

Unopened vial
3 years

After first opening
Once transferred from the vial into the syringe, the solution of MabThera subcutaneous formulation is physically and chemically stable for 48 hours at 2 °C - 8 °C and subsequently for 8 hours at 30°C in di**f** use daylight.

From a microbiological point ofview, the product should be used immediately. Ifnot used immediately, preparation should take place in controlled and validated aseptic conditions. In-use storage times and conditions prior to use are the responsibility ofthe user.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C). Keep the container in the outer carton in order to protect from light.
For storage conditions after first opening see section 6.3.

6.5 Nature and contents ofcontainer

Colourless type I glass vial with butyl rubber stopper with aluminium over seal and a pink plastic flip-offdisk, containing 1400 mg/11.7 mL ofrituximab.

Each carton contains one vial.

6.6 Special precautions for disposal and other handling

MabThera is provided in sterile, preservative-free, non-pyrogenic, single use vials. Use sterile needle and syringe to prepare MabThera. A peel-off sticker is included on the vials which specifies the strength, route ofadministration and indication. This sticker should be removed from the vial and stuck onto the syringe prior to use. The following points should be strictly adhered to regarding the use and disposal ofsyringes and other medicinal sharps:

- Needles and syringes should never be reused
- Place all used needles and syringes into a sharps container (puncture-proofdisposablecontainer).

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

7 MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

8 MARKETING AUTHORISATION NUMBER(S)

EU/1/98/067/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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

10 DATE OF REVISION OF THE TEXT

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

1 NAME OF THE MEDICINAL PRODUCT

MabThera 1600 mg solution for subcutaneous injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains 120 mg ofrituximab.

Each vial contains 1600 mg/ 13.4 mL rituximab.

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

For the full list ofexcipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

Clear to opalescent, colourless to yellowish liquid with pH of5.2 – 5.8 and osmolality of300 - 400 mOsmol/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

See section 5.1 for further information.

4.2 Posology and method ofadministration

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

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

Premedication with glucocorticoids should be considered ifMabThera is not given in combination with glucocorticoid-containing chemotherapy-.

<u>Posology</u>

The recommended dose of MabThera subcutaneous formulation used for adult patients is a subcutaneous injection at a fixed dose of1600 mg irrespective ofthe patient’s body surface area.

Before starting MabThera subcutaneous injections, all patients must always receive beforehand, a full dose ofMabThera by intravenous infusion, using MabThera intravenous formulation (see section 4.4).

Ifpatients were not able to receive one full MabThera intravenous infusion dose prior to the switch, they should continue the subsequent cycles with MabThera intravenous formulation until a full intravenous dose is successfully administered.
Therefore, the switch to MabThera subcutaneous formulation can only occur at the second or subsequent cycles oftreatment.

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

MabThera subcutaneous formulation is not intended for intravenous administration and should be given via subcutaneous injection only. The 1600 mg strength is intended for subcutaneous use in CLL only.

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

The recommended dosage of MabThera in combination with chemotherapy for previously untreated and relapsed/refractory patients is: MabThera intravenous formulation 375 mg/m^2 body surface area administered on day 0 ofthe first cycle oftreatment followed by MabThera subcutaneous formulation injected at a fixed dose of1600 mg per cycle, on day 1 ofeach subsequent cycle (in total: 6 cycles). The chemotherapy should be given after MabThera administration.

Dose adjustments during treatment

No dose reductions of MabThera are recommended. When MabThera is given in combination with chemotherapy, standard dose reductions for the chemotherapeutic medicinal products should be applied (see section 4.8).

Special populations

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

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

Method ofadministration

Subcutaneous injections
MabThera 1600 mg subcutaneous formulation should be administered as subcutaneous injection only, over approximately 7 minutes. The hypodermic injection needle must only be attached to the syringe immediately prior to administration to avoid potential needle clogging.

MabThera subcutaneous formulation should be injected subcutaneously into the abdominal wall and never into areas where the skin is red, bruised, tender, hard or areas where there are moles or scars.

No data are available on performing the injection in other sites ofthe body, therefore injections should be restricted to the abdominal wall.

During the treatment course with MabThera subcutaneous formulation, other medicinal products for subcutaneous administration should preferably be given at different sites.

Ifan injection is interrupted it can be resumed at the same site or another location may be used, if appropriate.

Intravenous infusion administration
The Summary of Product Characteristics (SmPC) of MabThera 100 mg and 500 mg concentrate for solution for infusion should be referred to for information on dosing instructions and method of administration.

4.3 Contraindications

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

Active, severe infections (see section 4.4).

Patients in a severely immunocompromised state.

4.4 Special warnings and precautions for use

Treacibility

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

The information provided in the section 4.4 pertains to the use of MabThera subcutaneous formulation in the approved indications *Treatment of non-Hodgkin's lymphoma* (strength 1400 mg) and *Treatment of CLL* (strength 1600 mg). For information related to the other indications, please refer to the SmPC ofMabThera intravenous formulation.

Progressive multifocal leukoencephalopathy

Use of MabThera may be associated with an increased risk ofprogressive multifocal leukoencephalopathy (PML). Patients must be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML. If PML is suspected, further dosing must be suspended until PML has been excluded. The clinician should evaluate the patient to determine ifthe symptoms are indicative ofneurological dysfunction, and ifso, whether these symptoms are possibly suggestive of PML. Consultation with a neurologist should be considered as clinically indicated.

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

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

Ifa patient develops PML, the dosing of MabThera must be permanently discontinued.

Following reconstitution ofthe immune system in immunocompromised patients with PML, stabilisation or improved outcome has been seen. It remains unknown ifearly detection of PML and suspension ofMabThera therapy may lead to similar stabilisation or improved outcome.

Infusion/Administration-related reactions

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

This set ofreactions which includes syndrome ofcytokine release, tumor lysis syndrome and anaphylactic and hypersensitivity reactions are described below. They are not specifically related to the route ofadministration ofMabThera and can be observed with both formulations.

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

Severe cytokine release syndrome is characterised by severe dyspnea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. This syndrome may be associated with some features oftumour lysis syndrome such as hyperuricaemia, hyperkalaemia, hypocalcaemia, hyperphosphaetemia, acute renal failure, elevated lactate dehydrogenase (LDH) and may be associated with acute respiratory failure and death. The acute respiratory failure may be accompanied by events such as pulmonary interstitial infiltration or oedema, visible on a chest X-ray. The syndrome frequently manifests itselfwithin one or two hours ofinitiating the first infusion. Patients with a history ofpulmonary insufficiency or those with pulmonary tumour infiltration may be at greater risk ofpoor outcome and should be treated with increased caution. Patients who develop severe cytokine release syndrome should have their infusion interrupted immediately (see section 4.2) and should receive aggressive symptomatic treatment. Since initial improvement ofclinical symptoms may be followed by deterioration, these patients should be closely monitored until tumour lysis syndrome and pulmonary infiltration have been resolved or ruled out. Further treatment ofpatients after complete resolution ofsigns and symptoms has rarely resulted in repeated severe cytokine release syndrome.

Patients with a high tumour burden or with a high number ($\geq 25 \times 10^9$/L) ofcirculating malignant cells, such as patients with CLL who may be at higher risk ofespecially severe cytokine release syndrome, should be treated with extreme caution. These patients should be very closely monitored throughout the first infusion. Consideration should be given to the use ofa 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 ifthe lymphocyte count is still $>25 \times 10^9$/L.

Anaphylactic and other hypersensitivity reactions have been reported following the intravenous administration ofproteins to patients. In contrast to cytokine release syndrome, true hypersensitivity reactions typically occur within minutes after starting infusion. Medicinal products for the treatment of hypersensitivity reactions, e.g., epinephrine (adrenaline), antihistamines and glucocorticoids, should be available for immediate use in the event ofan allergic reaction during administration of MabThera. Clinical manifestations ofanaphylaxis may appear similar to clinical manifestations ofthe cytokine release syndrome (described above). Reactions attributed to hypersensitivity have been reported less frequently than those attributed to cytokine release.

Additional reactions reported in some cases were myocardial infarction, atrial fibrillation, pulmonary oedema and acute reversible thrombocytopenia.

Since hypotension may occur during MabThera administration, consideration should be given to withholding anti-hypertensive medicines 12 hours prior to giving MabThera.

Infusion related adverse reactions ofall kinds have been observed in 77% ofpatients treated with MabThera intravenous formulation (including cytokine release syndrome accompanied by hypotension and bronchospasm in 10 % ofpatients) see section 4.8. These symptoms are usually

reversible with interruption of MabThera infusion and administration ofan anti-pyretic, an antihistaminic, and, occasionally, oxygen, intravenous saline or bronchodilators, and glucocorticoids if required. Please see cytokine release syndrome above for severe reactions.

Administration related reactions have been observed in up to 50% ofpatients treated with MabThera subcutaneous formulation in clinical trials. The reactions occurring within 24 hours ofthe subcutaneous injection consisted primarily oferythema pruritus, rash and injections site reactions such as pain, swelling and redness and were generally ofmild or moderate (grade 1 or 2) and transient nature (see section 4.8).

Local cutaneous reactions were very common in patients receiving MabThera subcutaneous in clinical trials. Symptoms included pain, swelling, induration, haemorrhage, erythema, pruritus and rash (see section 4.8). Some local cutaneous reactions occurred more than 24 hours after the MabThera subcutaneous administration. The majority oflocal cutaneous reactions seen following administration of MabThera subcutaneous formulation was mild or moderate and resolved without any specific treatment.

Before starting MabThera subcutaneous injections, all patients must always receive beforehand, a full dose of MabThera by intravenous infusion, using MabThera intravenous formulation. The highest risk ofexperiencing an administration related reaction is generally observed at cycle one. Beginning the therapy with MabThera intravenous infusion would allow a better handling ofthe administration reactions by slowing or stopping the intravenous infusion.

Ifpatients were not able to receive one full MabThera intravenous infusion dose prior to the switch, they should continue the subsequent cycles with MabThera intravenous formulation until a full intravenous dose is successfully administered. Therefore, the switch to MabThera subcutaneous formulation can only occur at the second or subsequent cycles oftreatment.

As with the intravenous formulation, MabThera subcutaneous formulation should be administered in an environment where full resuscitation facilities are immediately available and under the close supervision ofan experienced healthcare professional. Premedication consisting ofan analgesic/antipyretic and an antihistamine should always be administered before each dose of MabThera subcutaneous formulation. Premedication with glucocorticoids should also be considered.

Patients should be observed for at least 15 minutes following MabThera subcutaneous administration. A longer period may be appropriate in patients with an increased risk of hypersensitivity reactions.

Patients should be instructed to contact their treating physician immediately ifsymptoms that are suggestive ofsevere hypersensitivity or cytokine release syndrome occur at any time after medicinal product administration.

Cardiac disorders

Angina pectoris, cardiac arrhythmias such as atrial flutter and fibrillation, heart failure and/or myocardial infarction have occurred in patients treated with MabThera. Therefore patients with a history ofcardiac disease and/or cardiotoxic chemotherapy should be monitored closely.

Haematological toxicities

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

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

Infections

Serious infections, including fatalities, can occur during therapy with MabThera (see section 4.8). MabThera should not be administered to patients with an active, severe infection (e.g. tuberculosis, sepsis and opportunistic infections, see section 4.3).

Physicians should exercise caution when considering the use of MabThera in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection (see section 4.8).

Cases ofhepatitis B reactivation have been reported in patients receiving the MabThera intravenous formulation including fulminant hepatitis with fatal outcome. The majority ofthese patients were also exposed to cytotoxic chemotherapy. Limited information from one study in relapsed/refractory CLL patients suggests that MabThera treatment may also worsen the outcome ofprimary hepatitis B infections. Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with MabThera. At minimum this should include HBsAg-status and HBcAb-status. These can be complemented with other appropriate markers as per local guidelines. Patients with active hepatitis B disease should not be treated with MabThera. Patients with positive hepatitis B serology (either HBsAg or HBcAb) should consult liver disease experts before start oftreatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation.

Very rare cases of PML have been reported during post-marketing use ofthe MabThera intravenous formulation in CLL (see section 4.8). The majority ofpatients had received rituximab in combination with chemotherapy or as part ofa hematopoietic stem cell transplant.

Immunisation

The safety ofimmunisation with live viral vaccines, following MabThera therapy has not been studied for NHL and CLL patients and vaccination with live virus vaccines is not recommended. Patients treated with MabThera may receive non-live vaccinations; however, with non-live vaccines response rates may be reduced. In a non-randomized study, patients with relapsed low-grade NHL who received the MabThera intravenous formulation as monotherapy when compared to healthy untreated controls had a lower rate ofresponse to vaccination with tetanus recall antigen (16% vs. 81%) and Keyhole Limpet Haemocyanin (KLH) neoantigen (4% vs. 69% when assessed for >2-fold increase in antibody titer). For CLL patients similar results are assumable considering similarities between both diseases, but this has not been investigated in clinical trials.

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

Skin reactions

Severe skin reactions such as Toxic Epidermal Necrolysis (Lyell's Syndrome) and Stevens - Johnson syndrome, some with fatal outcome, have been reported (see section 4.8). In case ofsuch an event, with suspected relationship to MabThera, treatment should be permanently discontinued.

4.5 Interaction with other medicinal products and other forms ofinteraction

Currently, there are limited data on possible drug interactions with MabThera.

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

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

4.6 Fertility, pregnancy and lactation

Contraception in males and females

Due to the long retention time ofrituximab in B cell depleted patients, women ofchildbearing potential must employ effective contraceptive methods during and for 12 months after treatment with MabThera.

Pregnancy

IgG immunoglobulins are known to cross the placental barrier.

B-cell levels in human neonates following maternal exposure to MabThera have not been studied in clinical trials. There are no adequate and well-controlled data from studies in pregnant women, however transient B-cell depletion and lymphocytopenia have been reported in some infants born to mothers exposed to MabThera during pregnancy. Similar effects have been observed in animal studies (see section 5.3).For these reasons MabThera should not be administered to pregnant women unless the possible benefit outweighs the potential risk.

Breast-feeding

Limited data on rituximab excretion into breast milk suggest very low milk levels (relative infant dose less than 0.4%). Few cases of follow-up ofbreastfed infants describe normal growth and development up to 1.5 years. However, as these data are limited and the long-term outcomes of breastfed infants remain unknown, breastfeeding is not recommended while being treated with rituximab and optimally for 12 months following rituximab treatment.

Fertility

Animal studies did not reveal deleterious effects ofrituximab or recombinant human hyaluronidase (rHuPH20) on reproductive organs.

4.7 Effects on ability to drive and use machines

No studies on the effects of MabThera on the ability to drive and use machines have been performed, although the pharmacological activity and adverse reactions reported to date suggest that MabThera would have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The information provided in this section pertains to the use ofMabThera in oncology.
For information related to the autoimmune indications, please refer to the SmPC of MabThera intravenous formulation.

Summary ofthe safety profile

During the development programme, the safety profile of MabThera subcutaneous formulation was comparable to that ofthe intravenous formulation with the exception oflocal cutaneous reactions. Local cutaneous reactions including injection site reactions were very common in patients receiving

MabThera subcutaneous formulation. In the NHL phase 3 trial SABRINA (BO22334), local cutaneous reactions were reported in up to 20% ofpatients receiving subcutaneous MabThera. The most common local cutaneous reactions in the MabThera subcutaneous arm were injection site erythema (13%), injection site pain (7%), and injection site oedema (4%). Events seen following subcutaneous administration were mild or moderate, apart from one patient who reported a local cutaneous reaction

of Grade 3 intensity (injection site rash) following the first MabThera subcutaneous administration (Cycle 2). Local cutaneous reactions ofany grade in the MabThera subcutaneous arm were most common during the first subcutaneous cycle (Cycle 2), followed by the second, and the incidence decreased with subsequent injections. Similar events were observed in the CLL SAWYER trial (BO25341) and were reported in up to 42% ofpatients in the MabThera subcutaneous arm. Most common local cutaneous reactions were injection site erythema (26%), injection site pain (16%), and injection site swelling (5%). Two patients in SAWYER trial who experienced Grade 3 local cutaneous reactions (injection site erythema, injection site pain and injection site swelling).

Adverse reactions reported in MabThera subcutaneous formulation usage

The risk ofacute administration-related reactions associated with the subcutaneous formulation of MabThera was assessed in -three clinical trials: SparkThera and SABRINA (the two trials in NHL) and SAWYER the CLL trial.
In trial SABRINA, severe administration-related reactions (grade≥3) were reported in two patients (2%) following administration of MabThera subcutaneous formulation . These events were Grade 3 injection site rash and dry mouth.
In trial SparkThera, no severe administration-related reactions were reported.
In SAWYER (BO25341), severe administration-related reactions (Grade ≥3) were reported in four patients (5%) following MabThera subcutaneous administration. These events were Grade 4 thrombocytopenia and Grade 3 anxiety, injection-site erythema and urticaria.

Adverse reactions reported in MabThera intravenous formulation usage

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

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

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

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

The most frequent reported or observed serious adverse reactions were:

- Infusion-related reactions (including cytokine-release syndrome, tumour-lysis syndrome), seesection 4.4.
- Infections, see section 4.4.
- Cardiovascular disorders, see section 4.4.

Other serious ADRs reported include hepatitis B reactivation and PML (see section 4.4.).

The frequencies of ADRs reported with MabThera alone or in combination with chemotherapy are summarised in Table 1. Frequencies are defined as very common (³ 1/10), common (³ 1/100 to < 1/10), uncommon (³ 1/1,000 to < 1/100), rare (³ 1/10,000 to < 1/1000), very rare (< 1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order ofdecreasing seriousness.

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

Tabulated list ofadverse reactions

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

MedDRA System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not known
Infections and infestations	bacterial infections, viral infections, +bronchitis	sepsis, +pneumonia, +febrile infection, +herpes zoster, +respiratory tract infection, fungal infections, infections of unknown aetiology, +acute bronchitis, +sinusitis, hepatitis B[1]		serious viral infection[2]		
Blood and lymphatic system disorders	neutropenia, leucopenia, +febrile neutropenia, +thrombocytopenia	anaemia, +pancytopenia, +granulocytopenia	coagulation disorders, aplastic anaemia, haemolytic anaemia, lymphadenopathy		transient increase in serum IgM levels[3]	late neutropenia[3]
Immune system disorders	infusion related reactions[4], angioedema	hypersensitivity		anaphylaxis	tumour lysis syndrome, cytokine release syndrome[4], serum sickness	infusion-related acute reversible thrombocytopenia [4]
Metabolism and nutrition disorders		hyperglycaemia, weight decrease, peripheral oedema, face oedema, increased LDH, hypocalcaemia				
Psychiatric disorders			depression, nervousness,			
Nervous system disorders		paraesthesia, hypoaesthesia, agitation, insomnia, vasodilatation, dizziness, anxiety	dysgeusia		peripheral neuropathy, facial nerve palsy[5]	cranial neuropathy, loss ofother senses[5]
Eye disorders		lacrimation disorder, conjunctivitis			severe vision loss[5]	
Ear and labyrinth disorders		tinnitus, ear pain				hearing loss[5]

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

MedDRA System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not known
Investigations	decreased IgG levels					

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

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

[2] see also section infection below

[3] see also section haematologic adverse reactions below

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

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

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

[7] includes fatal cases

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

Signs and symptoms suggestive ofan infusion-related reaction were reported in more than 50 % of patients in clinical trials involving MabThera intravenous formulation, and were predominantly seen during the first infusion, usually in the first one to two hours. These symptoms mainly comprised fever, chills and rigors. Other symptoms included flushing, angioedema, bronchospasm, vomiting, nausea, urticaria/rash, fatigue, headache, throat irritation, rhinitis, pruritus, pain, tachycardia, hypertension, hypotension, dyspnoea, dyspepsia, asthenia and features oftumour lysis syndrome. Severe infusion-related reactions (such as bronchospasm, hypotension) occurred in up to 12 % ofthe cases. Additional reactions reported in some cases were myocardial infarction, atrial fibrillation, pulmonary oedema and acute reversible thrombocytopenia. Exacerbations ofpre-existing cardiac conditions such as angina pectoris or congestive heart failure or severe cardiac disorders (heart failure, myocardial infarction, atrial fibrillation), pulmonary oedema, multi-organ failure, tumour lysis syndrome, cytokine release syndrome, renal failure, and respiratory failure were reported at lower or unknown frequencies. The incidence ofinfusion-related symptoms decreased substantially with subsequent intravenous infusions and is <1% ofpatients by the eighth cycle of MabThera (containing) treatment.

Description ofselected adverse reactions

Infections

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

Localized candida infections as well as Herpes zoster were reported at a higher incidence in the MabThera-containing arm ofrandomized studies. Severe infections were reported in about 4% of patients treated with MabThera monotherapy. Higher frequencies ofinfections overall, including grade 3 or 4 infections, were observed during MabThera maintenance treatment up to 2 years when compared to observation. There was no cumulative toxicity in terms ofinfections reported over a 2-year treatment period. In addition, other serious viral infections either new, reactivated or exacerbated, some ofwhich were fatal, have been reported with MabThera treatment. The majority of patients had received MabThera in combination with chemotherapy or as part ofa hematopoietic stem cell transplant. Examples ofthese serious viral infections are infections caused by the herpes viruses (Cytomegalovirus, Varicella Zoster Virus and Herpes Simplex Virus), JC virus (PML) and hepatitis C virus. Cases of fatal PML that occurred after disease progression and retreatment have also been reported in clinical trials. Cases ofhepatitis B reactivation, have been reported, the majority ofwhich were in patients receiving MabThera in combination with cytotoxic chemotherapy. In patients with relapsed/refractory CLL, the incidence ofgrade 3/4 hepatitis B infection (reactivation and primary infection) was 2% in R-FC vs 0% in FC. Progression ofKaposi’s sarcoma has been observed in

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

Haematologic adverse reactions

In clinical trials with MabThera monotherapy given for 4 weeks, haematological abnormalities occurred in a minority ofpatients and were usually mild and reversible. Severe (grade 3/4) neutropenia was reported in 4.2%, anaemia in 1.1% and thrombocytopenia in 1.7% ofthe patients. During MabThera maintenance treatment for up to 2 years, leucopoenia (5% vs. 2%, grade 3/4) and neutropenia (10% vs. 4%, grade 3/4) were reported at a higher incidence when compared to observation. The incidence ofthrombocytopenia was low (<1 %, grade 3/4) and was not different between treatment arms. During the treatment course in studies with MabThera in combination with chemotherapy, grade 3/4 leucopoenia (R-CHOP 88% vs. CHOP 79%, R-FC 23% vs. FC 12%), grade 3/4 neutropenia (R-CVP 24% vs. CVP 14%; R-CHOP 97% vs. CHOP 88%, R-FC 30% vs. FC 19% in previously untreated CLL), grade 3/4 pancytopenia (R-FC 3% vs. FC 1% in previously untreated CLL) were usually reported with higher frequencies when compared to chemotherapy alone. However, the higher incidence ofneutropenia in patients treated with MabThera and chemotherapy was not associated with a higher incidence ofinfections and infestations compared to patients treated with chemotherapy alone. Studies with MabThera intravenous formulation in previously untreated and relapsed/refractory CLL have established that in up to 25% ofpatients treated with R-FC neutropenia was prolonged (defined as neutrophil count remaining below $1x10^9$/L between day 24 and 42 after the last dose) or occurred with a late onset (defined as neutrophil count below $1x10^9$/L later than 42 days after last dose in patients with no previous prolonged neutropenia or who recovered prior to day 42) following treatment with MabThera plus FC.There were no differences reported for the incidence ofanaemia. Some cases oflate neutropenia occurring more than four weeks after the last infusion of MabThera were reported. In the CLL first-line study, Binet stage C patients experienced more adverse events in the R-FC arm compared to the FC arm (R-FC 83% vs. FC 71%). In the relapsed/refractory CLL study grade 3/4 thrombocytopenia was reported in 11% ofpatients in the R-FC group compared to 9% ofpatients in the FC group.

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

Cardiovascular adverse reactions

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

Respiratorysystem

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

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

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

Gastrointestinal disorders
Gastrointestinal perforation in some cases leading to death has been observed in patients receiving MabThera for treatment of Non-Hodgkin's lymphoma (NHL). In the majority ofthese cases, MabThera was administered with chemotherapy.

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

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

Patient subpopulations - MabThera monotherapy
Elderly (³ 65 years):
The incidence of ADRs ofall grades and grade 3 /4 ADR was similar in elderly patients compared to younger patients (<65 years).

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

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

Patient subpopulations - MabThera combination therapy
Elderly (³ 65 years)
The incidence ofgrade 3/4 blood and lymphatic adverse events was higher in elderly patients compared to younger patients (<65 years), with previously untreated or relapsed/refractory CLL.

Reporting ofsuspected adverse reactions

Reporting suspected adverse reactions after authorisation ofthe medicinal product is important. It allows continued monitoring ofthe benefit/risk balance ofthe medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Limited experience with doses higher than the approved dose ofintravenous MabThera formulation is available from clinical trials in humans. The highest intravenous dose of MabThera tested in humans to date is 5000 mg (2250 mg/m^2), tested in a dose escalation study in patients with CLL. No additional safety signals were identified.
Patients who experience overdose should have immediate interruption oftheir infusion and be closely monitored.

Three patients in the MabThera subcutaneous NHL formulation trial SABRINA (BO22334) were inadvertently adminstered subcutaneous formulation through the intravenous route up to a maximum rituximab dose of 2780 mg with no untoward e**f** ect.
Patients who experience overdose or medication error with MabThera should be closely monitored.

In the post-marketing setting five cases of MabThera overdose have been reported. Three cases had no reported adverse event. The two adverse events that were reported were flu-like symptoms, with a dose of1.8 g ofrituximab and fatal respiratory failure, with a dose of 2 g ofrituximab.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

MabThera subcutaneous formulation contains recombinant human hyaluronidase (rHuPH20), an enzyme used to increase the dispersion and absorption ofco-administered substances when administered subcutaneously.

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

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

The Fab domain ofrituximab binds to the CD20 antigen on B lymphocytes and the Fc domain can recruit immune effector functions to mediate B cell lysis. Possible mechanisms ofeffector-mediated cell lysis include complement-dependent cytotoxicity (CDC) resulting from C1q binding, and antibody-dependent cellular cytotoxicity (ADCC) mediated by one or more ofthe Fc**g** receptors on the surface ofgranulocytes, macrophages and NK cells. Rituximab binding to CD 20 antigen on B lymphocytes has also been demonstrated to induce cell death via apoptosis.

Peripheral B cell counts declined below normal following completion ofthe first dose of MabThera. In patients treated for hematological malignancies, B cell recovery began within 6 months oftreatment and generally returned to normal levels within 12 months after completion oftherapy, although in some patients this may take longer (up to a median recovery time of 23 months post-induction therapy). In rheumatoid arthritis patients, immediate depletion ofB cells in the peripheral blood was

observed following two infusions of 1000 mg MabThera separated by a 14 day interval. Peripheral blood B cell counts begin to increase from week 24 and evidence for repopulation is observed in the majority ofpatients by week 40, whether MabThera was administered as monotherapy or in combination with methotrexate.

Clinical experience ofMabThera subcutaneous formulation in chronic lymphocytic leukaemia

A two-part phase Ib, multicenter, randomized, open-label, parallel-group trial (SAWYER BO25341) was conducted in patients with previously untreated CLL, to investigate the non-inferiority ofthe pharmacokinetic profile, together with efficacy and safety of MabThera subcutaneous formulation in combination with chemotherapy.

The objective ofthe Part 1 was to select a MabThera subcutaneous formulation dose that resulted in comparable MabThera serum C_{trough} levels compared with MabThera intravenous formulation. A total of 64 patients with CLL were enrolled at any point prior to cycle 5 during their treatment with MabThera intravenous formulation in combination with chemotherapy. The dose of 1600 mg of MabThera subcutaneous formulation was selected for the Part 2 ofthe study.

The objective ofthe Part 2 was to establish the non-inferiority in observed C_{trough} levels between the selected MabThera subcutaneous dose and the reference MabThera intravenous dose.
A total of176 patients with CLL were randomized into the following two treatment groups:

- MabThera subcutaneous (n= 88); 1st cycle of MabThera intravenous 375 mg/m^2 in combination with chemotherapy plus subsequent cycles (2-6) of MabThera subcutaneous1600mg in combination with chemotherapy.

- MabThera intravenous (n= 88); 1st cycle of MabThera intravenous 375 mg/m^2 in combinationwith chemotherapy followed by up to 5 cycles of MabThera intravenous 500 mg/m^2 in combination with chemotherapy.

The response rates for the analysis of176 patients in SAWYER Part 2 are shown in Table 2.

Table 2 Efficacy results for SAWYER (BO25341) (Intent to Treat Population)

		Part 2 N = 176	
		Rituximab intravenous formulation (n = 88)	Rituximab subcutaneous formulation (n = 88)
ORR[a]	Point estimate	80.7% (n = 71)	85.2% (n = 75)
	95% CI	[70.9%, 88.3%]	[76.1%, 91.9%]
CRR[a]	Point estimate	31.8% (n = 28)	27.3% (n = 24)
	95% CI	[22.3%, 42.6%]	[18.3%, 37.8%]
PFS[b]	Proportion with PFS event	42.0% (n = 37)	34.1% (n = 30)
	95% CI	0.76 [0.47%, 1.23%]	

ORR – Overall Response Rate
CRR – Complete Response Rate
PFS – Progression-Free Survival (proportion with event, disease progression/relapse or death from any cause)
[a] – at 3 month follow-up visit (Part 2)
[b] – at time offinal analysis (median follow-up 53 months)

Overall the results confirm that MabThera subcutaneous formulation 1600 mg has a comparable benefit/risk profile to that ofMabThera intravenous formulation 500 mg/m^2.

Immunogenicity

Data from the development programme of MabThera subcutaneous formulation indicate that the formation ofanti-rituximab antibodies after subcutaneous administration is comparable with that observed after intravenous administration. In SAWYER trial (BO25341) the incidence of treatment-induced/enhanced anti-rituximab antibodies was similar in the two treatment arms; 15% intravenous vs. 12% subcutaneous. The incidence oftreatment-induced/enhanced anti-rHuPH20 antibodies, only measured in patients in the subcutaneous arm was 12%. None ofthe patients who tested positive for anti-rHuPH20 antibodies tested positive for neutralizing antibodies.

The clinical relevance ofthe development ofanti-rituximab or anti-rHuPH20 antibodies after treatment with MabThera subcutaneous formulation is not known. There was no impact ofthe presence ofanti-rituximab or anti-rHuPH20 antibodies on safety, e**f** icacy or PK ofMabThera.

Clinical experience ofMabThera concentrate for solution for infusion in CLL

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 ofeach subsequent treatment cycle. Patients were excluded from the study in relapsed/refractory CLL ifthey had previously been treated with monoclonal antibodies or ifthey were refractory (defined as failure to achieve a partial remission for at least 6 months) to fludarabine or any nucleoside analogue. A total of 810 patients (403 R-FC, 407 FC) for the first-line study (Table 2a and Table 2b) and 552 patients (276 R-FC, 276 FC) for the relapsed/refractory study (Table 3) were analysed for efficacy.

In the first-line study, after a median observation time of48.1 months, the median PFS was 55 months in the R-FC group and 33 months in the FC group ($p < 0.0001$, log-rank test). The analysis ofoverall survival showed a significant benefit ofR-FC treatment over FC chemotherapy alone ($p = 0.0319$, log-rank test) (Table 2a). The benefit in terms of PFS was consistently observed in most patient subgroups analysed according to disease risk at baseline (i.e. Binet stages A-C) (Table 2b).

Table 2a First--line treatment ofchronic lymphocytic leukaemia
Overview of e**f** icacy results for MabThera plus FC vs. FC alone - 48.1 months median observation time

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

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

Table 2b First-line treatment ofchronic lymphocytic leukaemia

Hazard ratios of progression-free survival according to Binet stage (ITT) – 48.1 months median observation time

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

CI: Confidence Interval

In the relapsed/refractory study, the median progression-free survival (primary endpoint) was 30.6 months in the R-FC group and 20.6 months in the FC group (p=0.0002, log--rank test). The benefit in terms of PFS was observed in almost all patient subgroups analysed according to disease risk at baseline. A slight but not significant improvement in overall survival was reported in the R-FC compared to the FC arm.
No PK/clinical data are available in patients with a refractory or relapsing disease.

Table 3 Treatment of relapsed/refractory chronic lymphocytic leukaemia -overview of ef icacy results for MabThera plus FC vs. FC alone (25.3 months median observation time)

Efficacy Parameter	Kaplan--Meier Estimate of Median Time to Event (Months)			Risk Reduction
	FC (N = 276)	R--FC (N=276)	Log--Rank p value	
Progression--free survival (PFS)	20.6	30.6	0.0002	35%
Overall survival	51.9	NR	0.2874	17%
Event free survival	19.3	28.7	0.0002	36%
Response rate (CR, nPR, or PR)	58.0%	69.9%	0.0034	n.a.
CR rates	13.0%	24.3%	0.0007	n.a.
Duration ofresponse *	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 analysedusing Chi--squared Test.
*: only applicable to patients achieving a CR, nPR, PR; NR: not reached n.a. not applicable
**: only applicable to patients achieving a CR;

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

Paediatric population

The European Medicines Agency has waived the obligation to submit the results ofstudies with rituximab in all subsets ofthe paediatric population with CLL. See Section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Absorption

MabThera at a fixed dose of 1600 mg was administered for 5 cycles subcutaneously at 4-weekly intervals, following the first cycle of MabThera intravenous formulation, in previously untreated CLL patients in combination with chemotherapy (fludarabine and cyclophosphamide (FC). The serum MabThera C_{max} at Cycle 6 was lower in the subcutaneous arm than the intravenous, with geometric mean (CV%) values of 202 (36.1) µg/mL and 280 (24.6) µg/mL with the resulting geometric mean ratio ($C_{max, SC}/C_{max, IV}$) of 0.719 (90% CI: 0.653, 0.792). The geometric mean t_{max} in the MabThera subcutaneous group was approximately 3 days as compared to the t_{max} occuring at or close to the end ofthe infusion for the MabThera intravenous group. The geometric mean C_{trough} (CV%) values at Cycle 5 (pre-dose Cycle 6) were higher among the MabThera subcutaneous group than the MabThera intravenous group; 97.5 mg/mL (42.6) versus 61.5 mg/mL (63.9) respectively with a resulting adjusted geometric mean ratio [90% CI] of 1.53 [1.27-1.85]. Similarly, the geometric mean AUC (CV%) values at Cycle 6 were higher among the subcutaneous group than the intravenous group; 4088 µg·day/mL (34.2) versus 3630 µg·day/mL (32.8) respectively) with a resulting adjusted geometric mean ratio [90% CI] of 1.10 [0.98-1.24].
Based on popPK analysis ofstudy BO25341 (SAWYER) an absolute bioavailability of 68.4% was estimated.

Distribution/Elimination

The estimated half-life of Mabthera subcutaneous formulation of 1600 mg is 30 days, the estimated clearance is 0.22 L/day and the volume ofdistribution ofthe central compartment is 4.65 L.

Special populations

As typical for monoclonal antibodies, rituximab PK parameters depended on body size measures. All clearance and volume parameters increased with BSA. In addition, central volume was slightly (9%) lower in females compared to males. Absorption parameters ofsubcutaneous formulation, decreased with increasing BMI. Conditional simulations that summarized the impact ofall body size dependencies on rituximab exposure demonstrated that, while fixed subcutaneous dosing leads to larger differences in exposure (C_{trough} and AUC_{τ}) between subjects with low and high body sizes compared to body-weight-adjusted intravenous dosing, it allows to maintain C_{trough} and AUC_{τ} values for all body-size groups at the levels not lower than levels attained by intravenous dosing, thus achieving at least the same target saturation as for intravenousdosing. For subjects weighing > 90 kg, C_{trough} values were the same for the intravenous and subcutaneous regimens. For subjects weighing 60-90 kg and < 60 kg, average C_{trough} values following intravenous dosing were approximately 16% and 34% lower compared to the subcutaneous regimen, respectively. Similarly, for subjects in the high BSA tritile, C_{trough} values were the same for the intravenous and subcutaneous regimens. For subjects in the middle and low BSA tritiles, average C_{trough} values following intravenous dosing were approximately 12% and 26% lower compared to the subcutaneous regimen.

In addition to dependence on body size, time-dependent clearance was higher in subjects with higher baseline tumour size, which is consistent with target-mediated elimination. Higher time-dependenet clearance in subjects with higher disease burden would lead to lower initial exposure and longer time needed to achieve the same exposure as in subjects with lower burden ofthe disease.

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 oftoxicity to the foetus due to rituximab. However, dose-dependent pharmacologic depletion of B cells in the lymphoid organs ofthe 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 ofbirth and did not compromise the reaction to immunization.

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 ofrituximab.
Specific studies to determine the e**f** ects ofrituximab or rHuPH20 on fertility have not been performed. In general toxicity studies in cynomolgus monkeys no deleterious e**f** ects on reproductive organs in males or females were observed. Additionally, no effects on semen quality were shown for rHuPH20.

In embryofetal developmental studies in mice, rHuPH20 caused reduced fetal weight and loss of implantations at systemic exposures su**f** iciently in excess ofhuman therapeutic exposure.
There is no evidence ofdysmorphogenesis (i.e. teratogenesis) resulting from systemic exposure to rHuPH20.

6 PHARMACEUTICAL PARTICULARS

6.1 List ofexcipients

Recombinant human hyaluronidase (rHuPH20)
L-histidine
L-histidine hydrochloride monohydrate
a,a-trehalose dihydrate
L-methionine
Polysorbate 80 (E433)
Water for injections

6.2 Incompatibilities

No incompatibilities between MabThera subcutaneous formulation and polypropylene or polycarbonate syringe material or stainless steel transfer and injection needles and polyethylene Luer cone stoppers have been observed.

6.3 Shelflife

Unopened vial
3 years

After first opening
Once transferred from the vial into the syringe, the solution of MabThera subcutaneous formulation is physically and chemically stable for 48 hours at 2 °C - 8 °C and subsequently for 8 hours at 30°C in di**f** use daylight.

From a microbiological point ofview, the product should be used immediately. Ifnot used immediately, preparation should take place in controlled and validated aseptic conditions. In-use storage times and conditions prior to use are the responsibility ofthe user.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C). Keep the container in the outer carton in order to protect from light.
For storage conditions after first opening see section 6.3.

6.5 Nature and contents ofcontainer

Colourless type I glass vial with butyl rubber stopper with aluminium over seal and a blue plastic flip-offdisk, containing 1600 mg/13.4 mL ofrituximab.

Each carton contains one vial.

6.6 Special precautions for disposal and other handling

MabThera is provided in sterile, preservative-free, non-pyrogenic, single use vials. Use sterile needle and syringe to prepare MabThera. A peel-off sticker is included on the vials which specifies the strength, route ofadministration and indication. This sticker should be removed from the vial and stuck onto the syringe prior to use. The following points should be strictly adhered to regarding the use and disposal ofsyringes and other medicinal sharps:

- Needles and syringes should never be reused
- Place all used needles and syringes into a Sharps container (puncture-proofdisposablecontainer).

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

7 MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

8 MARKETING AUTHORISATION NUMBER(S)

09113/08507/REN/2022

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:
Date oflatest renewal: Nov 23, 2023

10 DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website ofthe European Medicines