ROCHE

MabThera®

Composition

Active substances

Rituximab (produced by recombinant DNA technology using CHO [Chinese hamster ovary] cells).

Excipients

Polysorbate 80 (produced from genetically modified maize), sodium chloride, sodium citrate, sodium hydroxide, hydrochloric acid, water for injection.
Each 10 ml vial of concentrate contains 52.6 mg of sodium; each 50 ml vial of concentrate contains 263 mg of sodium.

Pharmaceutical form and active substance quantity per unit

1 rubber-stoppered vial with 10 ml concentrate for solution for infusion contains 100 mg rituximab.

1 rubber-stoppered vial with 50 ml concentrate for solution for infusion contains 500 mg rituximab.

Indications/Uses

Non-Hodgkin's lymphoma (NHL)

Monotherapy in adult patients with CD20-positive follicular non-Hodgkin's lymphoma (stage III-IV) who have relapsed after, or failed to respond to, chemotherapy.

Treatment of previously untreated adult patients with CD20-positive follicular non-Hodgkin's lymphoma (stage III-IV) with high tumour burden in combination with CVP or CHOP. Responders may be administered maintenance therapy with rituximab monotherapy for 2 years.

Maintenance therapy of adult patients with relapsed or refractory CD20-positive follicular non-Hodgkin's lymphoma (stage III-IV) who have responded to induction therapy with CHOP with or without rituximab.

Treatment of adult patients with CD20-positive diffuse large B cell non-Hodgkin's lymphoma (DLBCL) in combination with standard CHOP (8 cycles of cyclophosphamide, doxorubicin, vincristine and prednisone).

Use in combination with fludarabine and cyclophosphamide (R-FC) for adult patients requiring treatment for chronic lymphocytic leukaemia (CLL). Patients previously treated with fludarabine should have responded for a period of at least 6 months.

Treatment, in combination with chemotherapy, of previously untreated paediatric patients (aged ≥6 months to <18 years) with advanced CD20-positive diffuse large B-cell non-Hodgkin lymphoma (DLBCL), Burkitt lymphoma (BL)/Burkitt leukaemia (mature B-cell acute leukaemia – BAL) or Burkitt-like lymphoma (BLL) (see "Dosage/Administration" and "Warnings and precautions").

Rheumatoid arthritis (RA)

MabThera in combination with methotrexate (MTX) is indicated for the treatment of adult patients with moderately severe to severe active rheumatoid arthritis after failure of one or more tumour necrosis factor (TNF) inhibitor therapies.

ANCA-associated vasculitis (AAV): Granulomatosis with polyangiitis/microscopic polyangiitis (GPA/MPA)

MabThera, in combination with corticosteroids, is indicated for the treatment of adult patients with severe active ANCA-associated vasculitis (granulomatosis with polyangiitis [GPA, also known as Wegener's granulomatosis] and microscopic polyangiitis [MPA]).

MabThera, in combination with glucocorticoids, is indicated for the induction of remission in paediatric patients (aged ≥2 to <18 years) with severe active granulomatosis with polyangiitis (GPA) and with microscopic polyangiitis (MPA).

Pemphigus vulgaris (PV)

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

Dosage/Administration

MabThera infusions should be administered in a medical facility in which the resources for effective resuscitation can be immediately deployed. The infusions should be administered under the direct supervision of a physician experienced in the respective specialty. MabThera can be administered in an outpatient setting. Patients who develop respiratory symptoms or hypotension should be monitored for at least 24 hours.

MabThera is administered after dilution as an i.v. infusion through a dedicated line. MabThera must not be injected i.v. undiluted, nor may the prepared solution for infusion be administered as a bolus infusion. To ensure the traceability of biological medicinal products, it is recommended that the trade name and batch number be documented with every treatment.

Premedication in adult patients for all indications

Premedication consisting of an analgesic/antipyretic (e.g. paracetamol/acetaminophen) and an antihistamine (e.g. diphenhydramine) should always be given before each administration of MabThera.

Premedication with glucocorticoids should also be considered, in particular if MabThera is not given in combination with steroid-containing chemotherapy in patients with non-Hodgkin's lymphoma (see "Warnings and precautions").

Dose adjustments during treatment:

Reducing the dose of MabThera is not recommended. When MabThera is given in combination with chemotherapy, standard dose reductions should be applied for the chemotherapy agents.

Initiation of treatment in general

First infusion in adult patients:

The recommended initial infusion rate is 50 mg/h; after the first 60 minutes the rate can be escalated in 50 mg/h increments every 30 minutes to a maximum of 400 mg/h.

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

Dose adjustment following undesirable effects/interactions

Patients should be closely monitored for the onset of cytokine release syndrome (see "Warnings and precautions"). In patients who develop evidence of severe adverse drug reactions (ADRs), especially severe dyspnoea, bronchospasm or hypoxia, the infusion should be interrupted immediately. Patients with follicular non-Hodgkin's lymphoma, DLBCL or CLL should also be evaluated for evidence of tumour lysis syndrome. Patients with pre-existing respiratory failure or pulmonary tumour infiltration must undergo a chest x-ray. In all patients the infusion should not be restarted until all clinical signs and symptoms have fully resolved and laboratory values have returned to normal, at which point the infusion can be resumed at up to half the previous rate. If the same severe adverse drug reactions recur, consideration should be given to stopping the treatment.

Non-Hodgkin's lymphoma (NHL)

Follicular non-Hodgkin's lymphoma

Monotherapy: The recommended dosage is 375 mg/m^2 body surface area weekly for 4 weeks as an intravenous infusion.

Combination therapy: The recommended dosage of MabThera in combination with CVP or CHOP chemotherapy is 375 mg/m^2 body surface area once per cycle for 8 treatment cycles. The dose of MabThera is given on day 1 of each chemotherapy cycle after oral administration of the glucocorticoid component of the chemotherapy.

Maintenance therapy

In untreated patients, MabThera is administered every 2 months (375 mg/m² body surface area) until disease progression or up to a maximum duration of two years (12 infusions in total).

In relapsed or refractory patients who have responded to induction therapy, MabThera is administered every 3 months (375 mg/m² body surface area) until disease progression or up to a maximum duration of two years (8 infusions in total).

Diffuse large B cell non-Hodgkin's lymphoma

In patients with diffuse large B cell non-Hodgkin's lymphoma, MabThera should be used in combination with CHOP chemotherapy.

The recommended dosage of MabThera is 375 mg/m^2 body surface area once every 3 weeks for 8 treatment cycles. The dose of MabThera is administered on day 1 of each chemotherapy cycle after i.v. administration of the glucocorticoid component of the CHOP chemotherapy.

Chronic lymphocytic leukaemia (CLL)

It is recommended that 48 hours before the start of treatment, prophylaxis with adequate fluid intake and administration of urostatic agents be initiated in order to reduce the risk of tumour lysis syndrome.

In addition, consideration should be given to premedication with glucocorticoids shortly before the start of the infusion with MabThera in order to reduce the frequency and severity of acute infusion-related reactions (IRRs) and/or of cytokine release syndrome.

The recommended dose of MabThera in previously untreated or relapsed/refractory CLL patients is 375 mg/m^2 body surface area on day 1 of the first treatment cycle, followed by 500 mg/m^2 body surface area on day 1 of cycles 2-6 (at four-week intervals). Fludarabine 25 mg/m^2 and cyclophosphamide 250 mg/m^2 are given on days 2, 3 and 4 in the first cycle and days 1-3 in cycles 2-6.

The following dosage adjustments are recommended if severe infections occur or if grade 3 or 4 cytopenia (anaemia, neutropenia, thrombocytopenia) that is not indicative of bone marrow involvement occurs on day 28 of a cycle:

Treatment can be postponed for 2 weeks and the dose of fludarabine and cyclophosphamide reduced by 25% in the following cycles.

In the event that after this first dose reduction a second episode of grade 3 or 4 cytopenia occurs on day 28 of a cycle independently of bone marrow involvement, treatment can once again be postponed by up to 2 weeks and the dose of fludarabine and cyclophosphamide can be reduced by a further 25%. This results in a dose equivalent to 50% of the normal fludarabine/cyclophosphamide dose.

Rheumatoid arthritis

Premedication with glucocorticoids should also be administered to decrease the incidence and severity of IRRs. Patients should receive 100 mg methylprednisolone i.v. to be completed 30 minutes prior to each MabThera infusion (see “Warnings and precautions”).

A treatment cycle with MabThera consists of two i.v. infusions of 1000 mg given at an interval of 2 weeks. Depending on the course of the disease, additional treatment cycles can be given.

First infusion:

The recommended initial infusion rate is 50 mg/h; after the first 30 minutes the rate can be escalated in 50 mg/h increments every 30 minutes to a maximum of 400 mg/h. This corresponds to an infusion time of 4 hours 15 minutes.

Subsequent infusions of MabThera can be started at a rate of 100 mg/h and increased by 100 mg/h increments every 30 minutes to a maximum of 400 mg/h. This corresponds to an infusion time of 3 hours 15 minutes.

Alternative administration of subsequent infusions at a concentration of 4 mg/ml in a volume of 250 ml over 120 minutes:

If patients have not experienced a serious infusion-related adverse event with their previous infusion, the next infusion can be given over 2 hours. For this administration variant it is recommended that a solution for infusion be prepared with a concentration of 4 mg/ml in a volume of 250 ml (corresponding to 1 g MabThera in 250 ml of prepared solution for infusion). The infusion is started at a rate of 250 mg/h for the first 30 minutes and continued at 600 mg/h for the next 90 minutes. If infusion over 2 hours is tolerated, this infusion rate may be retained for subsequent infusions and cycles.

Patients with clinically significant cardiovascular disease, including arrhythmias, or with serious IRRs to prior biological therapy or to MabThera, should not be treated with the 2-hour alternative infusion.

After the infusion has been completed the intravenous line should be left in place for at least one hour so that if necessary drugs can be administered i.v. If no undesirable effects occur during this period the intravenous line can then be removed.

In a dose-finding study in a less treatment-resistant patient population that had failed to respond to treatment with DMARDs (disease-modifying antirheumatic drugs), treatment with 2 × 500 mg per cycle proved similarly effective as 2 × 1000 mg (in terms of the ACR20 endpoint). Doses of less than 2 × 500 mg per cycle were not investigated.

The requirement for further cycles should be assessed 24 weeks after the previous cycle on the basis of residual or recurrent disease activity. Retreatment should be given if residual disease activity exceeds a DAS28-ESR score of 2.6. If the DAS28-ESR score is less than 2.6, retreatment should be given as soon as disease activity increases again (to DAS28-ESR >2.6).

Treatment with MabThera should only be continued in patients whose DAS28-ESR score has decreased by at least 1.2 units after two treatment cycles.

If ≥52 weeks have elapsed since the last MabThera treatment cycle, the first infusion of the new cycle should be given at the same rate as that used for the first dose.

In patients previously treated with TNF inhibitors, treatment with etanercept must have been discontinued for at least 4 weeks, and with infliximab or adalimumab for at least 8 weeks, before starting MabThera treatment.

The use of MabThera is not recommended in methotrexate-naïve patients since a favourable benefit-risk ratio has not been demonstrated.

ANCA-associated vasculitis (GPA/MPA) in adults

Treatment should only be conducted by physicians experienced in the treatment of rheumatic and immunological diseases.

In patients with ANCA-associated vasculitis, *Pneumocystis jirovecii* pneumonia (PCP) prophylaxis is recommended as needed during and after MabThera treatment.

Adult induction of remission

The recommended dosage of MabThera for remission-induction therapy in adult patients with severe active GPA or MPA is 375 mg/m^2 body surface area, administered as an i.v. infusion once weekly for 4 weeks. For the treatment of severe vasculitis symptoms it is recommended that MabThera be combined with intravenous methylprednisolone 1000 mg daily for 1 to 3 days, followed by oral prednisone 1 mg/kg body weight/day (not to exceed 80 mg/day and to be tapered as rapidly as possible according to clinical need) during and after treatment with MabThera.

Adult maintenance treatment

Following induction of remission with MabThera, maintenance treatment in adult patients with GPA and MPA may 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 within 4 weeks of disease remission.

Any concomitant corticosteroid therapy should be tapered according to clinical judgment.

MabThera should be administered as two 500 mg intravenous infusions two weeks apart, followed by one 500 mg intravenous infusion after 6, 12 and 18 months, then every 6 months as required based on clinical assessment.

Pemphigus vulgaris (PV) in adults

The recommended dosage of MabThera for the treatment of pemphigus vulgaris is 1000 mg by intravenous infusion followed two weeks later by a second 1000 mg intravenous infusion in combination with tapering glucocorticoid therapy.

Pneumocystis jirovecii pneumonia (PCP) prophylaxis according to local clinical guidelines is recommended for adult patients with PV during and following MabThera treatment, if required.

Maintenance therapy

A 500 mg intravenous maintenance infusion should be administered after 12 and 18 months, then every 6 months as required based on clinical assessment. Corticosteroids should be tapered according to local guidelines and the physician's clinical judgment.

Treatment of relapse

In the event of relapse, patients may receive 1000 mg intravenously. 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 dosage instructions

Children and adolescents

Non-Hodgkin's lymphoma

Premedication

The safety and efficacy of MabThera in paediatric patients ≥6 months to <18 years of age have not been established in indications other than previously untreated advanced CD20-positive DLBCL/BL/BAL/BLL. Clinical data on children under 3 years of age are available from only one patient. The dosage recommendations for children 6 months to 3 years of age are based on simulated

pharmacokinetic data from a population PK model (see “Warnings and precautions”, “Undesirable effects” and “Pharmacokinetics”).
MabThera should not be used in paediatric patients <6 months of age with CD20-positive diffuse large B-cell lymphoma (see “Clinical efficacy” “CD20+ DLBCL/BL/BAL/BLL in paediatric patients”).

In paediatric patients with non-Hodgkin’s lymphoma, premedication with paracetamol and an H1 antihistamine (= diphenhydramine or equivalent) should be administered 30 to 60 minutes before the start of the infusion of MabThera. In addition, prednisone should be given as described in Table 1.
In paediatric patients ≥6 months to <18 years of age with previously untreated advanced 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 dose of MabThera is 375 mg/m² body surface area, administered as an intravenous infusion. No MabThera dose adjustments other than by body surface area are required.

Table 1: MabThera dosage in paediatric patients with non-Hodgkin’s lymphoma

Cycle	**Day of treatment**	**Administration details**
Prephase (COP)	No MabThera given	–
Induction phase 1 (COPDAM1)	Day -2 (corresponding to day 6 of the prephase) 1st MabThera infusion	During the first induction phase, prednisone is given as part of the chemotherapy, and should be administered prior to MabThera.
	Day 1 2nd MabThera infusion	MabThera is given 48 hours after the first infusion of MabThera.
Induction phase 2 (COPDAM2)	Day -2 3rd MabThera infusion	In the second induction phase, prednisone is not given at the same time as MabThera.
	Day 1 4th MabThera infusion	MabThera is given 48 hours after the third infusion of MabThera.
Consolidation phase 1 (CYM/CYVE)	Day 1 5th MabThera infusion	Prednisone is not given at the same time as MabThera.
Consolidation phase 2 (CYM/CYVE)	Day 1 6th MabThera infusion	Prednisone is not given at the same time as MabThera.

Cycle	Day of treatment	Administration details
Maintenance phase 1 (M1)	Days 25 to 28 of consolidation phase 2 (CYVE) No MabThera given	Starts when peripheral counts have recovered after consolidation phase 2 (CYVE) with ANC >1.0 × 10^9/l and platelets >100 × 10^9/l
Maintenance phase 2 (M2)	Day 28 of maintenance phase 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 paediatric patients with non-Hodgkin's lymphoma: Concomitant chemotherapy with MabThera

Treatment plan	Patient staging	Administration details
Group B	Stage III with high LDH level (>N × 2), Stage IV CNS-negative	Prephase followed by 4 phases: 2 induction phases (COPADM) with HDMTX 3 g/m^2 and 2 consolidation phases (CYM)
Group C	Group C1: BAL CNS-negative, stage IV and BAL CNS-positive and CSF-negative	Prephase followed by 6 phases: 2 induction phases (COPADM) with HDMTX 8 g/m², 2 consolidation phases (CYVE) and 2 maintenance phases (M1 and M2)
	Group C3: BAL CSF-positive, stage IV CSF-positive	
Consecutive phases should be conducted as soon as blood counts recover and the patient's condition allows, except for the maintenance phases, which are conducted 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		

First infusion:

The recommended initial infusion rate is 0.5 mg/kg/h (maximum 50 mg/h); if no hypersensitivity or infusion-related reactions occur, it can be escalated by 0.5 mg/kg/h every 30 minutes to a maximum of 400 mg/h.

Subsequent infusions:

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

ANCA-associated vasculitis (GPA/MPA)

Clinical data on children and adolescents with ANCA-associated vasculitis are limited. There are no clinical data on children under 6 years of age. The dosage recommendations for children between 2 and 6 years of age are based on simulated pharmacokinetic data from a PK/PD model.

Premedication

Before the first MabThera i.v. infusion, paediatric patients with granulomatosis with polyangiitis or microscopic polyangiitis should be given i.v. methylprednisolone at a dosage of 30 mg/kg/day (no more than 1 g/day) for 3 days to treat severe symptoms of vasculitis. Up to three additional daily doses of 30 mg/kg i.v. methylprednisolone can be given based on clinical judgment, corresponding to a maximum of 6 daily doses.
Following completion of i.v. methylprednisolone administration, patients should be given oral prednisone 1 mg/kg/day (no more than 60 mg/day) and tapered if possible to 0.2 mg/kg/day (max. 10 mg/day) by month 6.
In patients with ANCA-associated vasculitis (GPA/MPA), *Pneumocystis jirovecii* pneumonia (PCP) prophylaxis is recommended as needed during and after MabThera treatment.

Induction of remission

The recommended dosage of MabThera for remission-induction therapy in paediatric patients with severe active GPA or MPA is 375 mg/m² body surface area, administered as an i.v. infusion once weekly for 4 weeks.

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 to childhood vaccinations against common, vaccine-preventable childhood diseases (e.g. measles, mumps, rubella and poliomyelitis) (see “Clinical efficacy” “Severe active ANCA-associated vasculitis [granulomatosis with polyangiitis (GPA) (Wegener’s granulomatosis) and microscopic polyangiitis (MPA)] in paediatric patients”).

Elderly patients

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

Patients with hepatic or renal impairment

No experience is available in patients with hepatic or renal impairment.

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed under “Composition”.

Patients with severe heart failure (NYHA class IV).

The combination of rituximab with chemotherapeutic agents including methotrexate during pregnancy and lactation.

Warnings and precautions

All indications

Progressive multifocal leukoencephalopathy

Cases of progressive multifocal leukoencephalopathy (PML) have been reported during or after the use of MabThera. Two cases of fatal PML in NHL patients were also observed in a clinical phase III study after disease progression and retreatment. The majority of patients had received MabThera in combination with chemotherapy or in a context of haematopoietic stem cell transplantation. In the differential diagnosis of patients developing neurological symptoms the possibility of PML must be considered.

Patients must be monitored at regular intervals for emergent or worsening symptoms indicative of PML. PML is frequently fatal and resistant to all therapy. PML signs and symptoms are varied, progress over days to weeks and may comprise increasing weakness in one side of the body or clumsiness in the limbs, loss of balance, visual disturbances and impairment of cognition, memory and orientation, leading to confusion and personality changes.

If in doubt, further investigations should be considered, including MRI (preferably contrast-enhanced), testing of the cerebrospinal fluid for JC virus DNA and serial neurological assessment. The physician should be alert to signs and symptoms indicative of PML, in particular those unnoticed by the patient (e.g. cognitive, neurological or psychiatric signs). The patient should in addition be advised to inform their partner or carers about their treatment since these persons may observe signs that escape the patient’s notice.

If PML is suspected, prompt neurological workup is indicated and treatment should be suspended until PML is excluded. If PML is confirmed, MabThera must be permanently withdrawn.

Following reconstitution of the immune system, stabilisation or improvement has been observed in immunosuppressed patients with PML. It is not known whether early detection of PML and suspension of MabThera treatment could lead to similar stabilisation or improvement.

Infusion reactions

Treatment with MabThera, especially administration of the first dose, may be associated with infusion reactions (IRRs) related to the release of cytokines and/or other chemical mediators. The incidence of

IRRs decreased from 77% (7% grade 3 and 4) with the first infusion to approximately 30% (2% grade 3 and 4) with the fourth infusion and to 14% (no grade 3 or 4 events) with the eighth infusion.

In general, the proportion of patients experiencing an IRR was higher after the first infusion of a cycle than after the second infusion. Subsequent MabThera cycles were better tolerated by patients than the first cycle.

Signs and symptoms that indicate an IRR are headache, itch, pyrexia, urticaria/rash, chills, pyrexia, sneezing, angioneurotic oedema, throat irritation, cough and bronchospasm – with or without associated hypotension or hypertension.

The reported reactions were generally reversible when the infusion of MabThera was administered more slowly or interrupted and an antipyretic, an antihistamine and – in isolated cases and if required – oxygen, i.v. saline solution or bronchodilators and glucocorticoids were administered.

It is recommended that IRRs be treated with diphenhydramine and paracetamol/acetaminophen. Additional treatment with bronchodilators or intravenous saline solution may be indicated.

Depending on the severity of the IRRs and measures required, MabThera may have to be temporarily or permanently withdrawn. In most cases the infusion can be continued with a 50% reduction of infusion rate (e.g. from 100 mg/hour to 50 mg/hour) after complete resolution of signs and symptoms. Most patients other than those with life-threatening IRRs were able to complete the treatment cycle with MabThera. Only rarely have severe IRRs recurred during subsequent treatment of patients whose signs and symptoms have resolved completely.

Severe IRRs may be clinically indistinguishable from hypersensitivity reactions or cytokine release syndrome. Severe IRRs with fatal outcome have been reported. Severe IRRs, which are characterised by pulmonary events, generally commence within 30 minutes to two hours after the start of the first MabThera infusion and in some cases have also included rapid tumour lysis and signs of tumour lysis syndrome as well as pyrexia, chills, rigors, hypotension, urticaria, angioedema and other signs and symptoms (see “Undesirable effects”).

Premedication consisting of an analgesic/antipyretic and an antihistamine should always be administered before each MabThera infusion. Premedication with glucocorticoids should also be administered to RA and CLL patients to decrease the incidence and severity of IRRs (see “Dosage/Administration”). Higher doses of intravenous glucocorticoids were administered in patients with ANCA-associated vasculitis.

In RA patients most of the IRRs reported in clinical studies were mild to moderate in severity. In clinical studies a severe infusion reaction occurred, independently of dose, in 14 of 3095 patients (<1%) with rheumatoid arthritis who received a first infusion of MabThera.

In post-marketing experience in RA, four severe IRRs have been reported with fatal outcome (in a total of approximately 150,000 treated RA patients). Patients with pre-existing heart disease and those with a history of previous unwanted cardiopulmonary effects should be closely monitored.

Infusion-related reactions in patients with ANCA-associated vasculitis and pemphigus vulgaris were comparable to those observed in RA patients.

Hypersensitivity reactions/anaphylaxis

The occurrence of anaphylactic and other hypersensitivity reactions has been reported after intravenous administration of proteins to patients. Adrenaline, antihistamines and glucocorticoids should be available for immediate use in the event of a hypersensitivity reaction to MabThera.

Pulmonary events

Pulmonary events including hypoxia, pulmonary infiltrates and acute respiratory failure have occurred. Some of these events were preceded by severe bronchospasm and dyspnoea. In some cases the signs and symptoms worsened over time, while in other cases an initial improvement was followed by a clinical deterioration. Patients with pulmonary events or other severe IRRs must therefore be closely monitored until their signs and symptoms have resolved completely. Patients with a history of respiratory failure or with pulmonary tumour infiltration are at greater risk of an unfavourable outcome and should therefore be treated with greater caution. Acute respiratory failure may be accompanied by events such as pulmonary interstitial infiltration or oedema, visible on a chest x-ray. The syndrome generally appears within one to two hours after the start of the first infusion. In patients with severe pulmonary events the infusion must be stopped immediately and symptomatic therapy initiated.

Cardiovascular system/heart failure

Since transient hypotension may occur during MabThera infusion, consideration should be given to withholding antihypertensive medications 12 hours prior to and throughout MabThera infusion. Cases of MabThera administration were observed in which pre-existing ischaemic heart disease became manifest and caused symptoms such as angina pectoris, myocardial infarction, atrial fibrillation and atrial flutter. Therefore, in patients with a history of heart disease, the risk of cardiovascular complications due to IRRs should be considered prior to treatment with MabThera. Patients with a history of heart disease (e.g. angina pectoris, cardiac arrhythmias such as atrial flutter or fibrillation, heart failure or myocardial infarction) should be closely monitored during the infusion. No data are available on the safety of MabThera in patients with moderately severe heart failure (NYHA class III). Patients with severe heart failure (NYHA class IV) should not be treated.

Monitoring of blood counts

Caution should be exercised when treating patients with neutrophil counts of <1.5 × 10^9/l and/or platelet counts of <75 × 10^9/l, as clinical experience with such patients is limited.

As with other tumour therapies, regular monitoring of full blood count, including platelet count, is indicated.

Preventive vaccinations

The physician should review vaccination status and follow local/national immunisation guidelines for adults against infectious diseases prior to treatment with MabThera. If possible, patients should receive any outstanding vaccinations in accordance with current immunisation guidelines before starting treatment with MabThera. The vaccinations should be completed at least four weeks prior to first administration of MabThera.

The safety of immunisation with vaccines, especially live vaccines, following MabThera therapy has not been studied, nor whether a primary humoral response to vaccines is possible. It is recommended that, if possible, all immunisations should be updated in line with current guidelines before starting treatment with MabThera.

Patients treated with MabThera must not receive live viral vaccines. If necessary, they may be immunised with non-live vaccines. Response to inactivated vaccines may be reduced during and after treatment with MabThera. In a non-randomised study, patients receiving MabThera monotherapy had a lower response rate (when assessed for a >2-fold increase in antibody titre) to testing with tetanus recall antigen (16% vs 81%) and keyhole limpet haemocyanin (KLH) (4% vs 76%), compared to untreated controls.

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

Patients treated with either MabThera and methotrexate or methotrexate alone showed similar response rates to tetanus recall antigen (39% vs 42%) and decreased response rates to a pneumococcal polysaccharide vaccine (43% vs 82%) 6 months after completing MabThera treatment.

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

Skin reactions

Severe mucocutaneous reactions, some with fatal outcome, have been reported in isolated patients treated with MabThera. These reactions occurred between 1 and 13 weeks after the start of treatment. Affected patients must receive no further infusions and undergo a medical examination immediately. A skin biopsy is useful for distinguishing between different skin reactions and determining subsequent treatment.

The mucocutaneous reactions reported included paraneoplastic pemphigus, lichenoid dermatitis and vesiculobullous dermatitis. Nothing is known regarding the safety of retreatment with MabThera in these cases.

Severe skin reactions, such as toxic epidermal necrolysis and Stevens-Johnson syndrome, some of which were fatal, have been reported (see “Undesirable effects”). In such an event, with a suspected relationship to MabThera, treatment should be permanently discontinued.

Infections

The risk of infection is potentially increased after treatment with MabThera. MabThera should not be administered to patients with active infection or severely impaired immune response (e.g. hypogammaglobulinaemia, severely reduced CD4 or CD8 cell counts). Caution is required when MabThera is prescribed for patients with a history of recurrent or chronic infection or an underlying disease that favours the occurrence of severe infections (see “Undesirable effects”). Patients who develop an infection after treatment with MabThera should be promptly investigated and appropriately treated.

Severe viral infections

Patients with severe viral infections should not be treated with MabThera. Severe viral infections, both new and reactivated or exacerbated, have been reported on treatment with rituximab and have been fatal in isolated cases. The majority of patients had received rituximab in combination with chemotherapy or in the context of haematopoietic stem cell transplantation. Examples of such severe viral infections include infections with herpes viruses (cytomegalovirus, varicella zoster virus, herpes simplex virus), JC virus (progressive multifocal leukoencephalopathy [PML]) and hepatitis B and C viruses.

Hepatitis B infection

Cases of hepatitis B reactivation – including fulminant hepatitis, sometimes with fatal outcome – have been reported; the majority of affected patients were also receiving cytotoxic chemotherapy. Causality cannot be clearly distinguished.

Hepatitis B virus (HBV) screening according to local guidelines should be performed in all patients before initiation of treatment with MabThera. At minimum this should include determination of HBsAg and anti-HBc, and should be complemented with other appropriate markers. Patients with active hepatitis B should not be treated with MabThera. Patients with positive hepatitis B serology should consult a liver disease specialist before the start of treatment and should be monitored and managed according to usual local standard medical practice to prevent hepatitis B reactivation.

Gastrointestinal tract

Gastrointestinal perforation or obstruction, in a few cases leading to death, has been observed in patients who received rituximab in combination with chemotherapy for the treatment of non-Hodgkin's lymphoma. Complaints of abdominal pain, especially at the start of treatment, should prompt a thorough diagnostic evaluation and appropriate treatment.

Nervous system disorders

There have been post-marketing reports of cases of posterior reversible encephalopathy syndrome (PRES)/reversible posterior leukoencephalopathy syndrome (RPLS). Signs and symptoms included visual disturbances, headaches, seizures and altered mental state with or without associated hypertension. The diagnosis of PRES/RPLS must be confirmed by brain imaging. In the reported cases there were recognised risk factors for PRES/RPLS including patients' underlying disease, hypertension, immunosuppressive therapy and/or chemotherapy.

Patients with haematological malignancies

Tumour lysis syndrome

MabThera brings about rapid lysis of benign and malignant CD20-positive cells and can precipitate tumour lysis syndrome with hyperuricaemia, hyperkalaemia, hypocalcaemia, hyperphosphataemia, elevated LDH levels and acute renal failure. Patients with a high number [>25,000/mm^3] of circulating malignant cells or a high tumour burden (lesions >10 cm) are at higher risk of tumour lysis syndrome and should be treated with extreme caution. In patients at risk for the development of tumour lysis syndrome the need for appropriate prophylaxis should be considered. In these patients the infusion rate should be reduced or infusion spread over two days in the first cycle, and in all subsequent cycles if the lymphocyte count remains above 25,000/mm^3. The patients should be monitored particularly closely during administration of the first infusion.

Paediatric patients

Only limited data are available for patients under 3 years of age. For further information, see "Clinical efficacy" "CD20+ DLBCL/BL/BAL/BLL in paediatric patients".

Non-Hodgkin's lymphoma in children 6 months to <3 years of age

In children aged 6 months to <3 years who were receiving treatment with rituximab (n=6), there were three cases of grade 4 sepsis and one of grade 4 Stevens-Johnson syndrome. In addition, all 6 patients had a serious event, including sepsis, Stevens-Johnson syndrome and tumour lysis syndrome.

Patients with rheumatoid arthritis and ANCA-associated vasculitis and pemphigus vulgaris

The efficacy and safety of MabThera for the treatment of autoimmune diseases other than rheumatoid arthritis, ANCA-associated vasculitis and pemphigus vulgaris have not been studied. An electrocardiogram should be performed before starting treatment of ANCA-associated vasculitis.

Further warnings and precautions

No data are available for patients with severe pulmonary disease. Caution should therefore be exercised when MabThera is used in these patients.

No data are available for patients with anaemia (Hb <8.5 g/dl) or neutropenia (neutrophil count <1500/µl).

Sodium content

This medicinal product contains 52.6 mg of sodium per 10 ml vial and 263.2 mg of sodium per 50 ml vial, corresponding to 2.63% and 13.16%, respectively, of the WHO-recommended maximum daily dietary sodium intake of 2 g for an adult.

Interactions

At present few data are available on possible drug interactions involving MabThera. In particular, interactions of rituximab in combination with chemotherapy (e.g. CHOP, CVP) have not been investigated.

Neither coadministration of fludarabine or cyclophosphamide with rituximab nor coadministration of methotrexate with rituximab has any effect on the pharmacokinetics of the individual components.

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

No pharmacokinetic or pharmacodynamic data are available on concomitant use of MabThera and TNF inhibitors. TNF inhibitors should not be administered for at least 8 weeks after completion of treatment with MabThera.

Pregnancy, lactation

Pregnancy

IgG immunoglobulins are known to cross the placental barrier. Because of the long retention time of MabThera in patients with B cell depletion, women of childbearing age in whom treatment is unavoidable and cannot be deferred should use a reliable method of contraception during treatment with MabThera and for 12 months thereafter.

Animal studies have shown no reproductive toxicity, although B cell-depleted populations have been found among neonates (see “Preclinical data”). No studies of B cell populations in human neonates after maternal exposure to MabThera have been performed. There are no adequate and well-controlled data on use in pregnant women, but transient B cell depletion and lymphocytopenia have been observed in some infants born to mothers exposed to rituximab during pregnancy. For these reasons MabThera must not be administered to pregnant women unless clearly necessary.

Lactation

It is not known whether rituximab is excreted in human milk. Given, however, that maternal IgG enters breast milk and animal studies have shown that rituximab is excreted into milk (see “Preclinical data”), women who are being treated with MabThera should not breastfeed.

Fertility

No clinical data are available on fertility with rituximab. Animal studies have revealed no evidence of impaired fertility with rituximab (see “Preclinical data”).

Effects on ability to drive and use machines

No relevant studies have been performed on the effects of MabThera on the ability to drive and use machines. The pharmacological action and the undesirable effects observed to date do not suggest the likelihood of any such effects. Nevertheless, the influence of premedication with antihistamines should be noted. After IRRs the patient’s condition should be allowed to stabilise before the patient drives vehicles or operates machines.

Undesirable effects

Experience from clinical studies in adults with NHL and CLL

Summary of the safety profile

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

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

In clinical trials, infections (predominantly bacterial and viral infections) occurred in approximately 30-55% of patients with NHL and in 30-50% of patients with CLL.

The most frequently reported or observed serious adverse reactions were:

- IRRs (including cytokine release syndrome, tumour lysis syndrome), see "Warnings and precautions".
- Infections, see "Warnings and precautions".
- Cardiovascular events, see "Warnings and precautions".

Other serious ADRs reported include hepatitis B reactivation and PML (see "Warnings and precautions").

The adverse drug reactions of all degrees of severity listed below are based on data from studies with approximately 2300 adults and 309 paediatric patients in whom MabThera was administered either as monotherapy/maintenance therapy or in combination with chemotherapy.

Within each frequency category, adverse drug reactions are listed in decreasing order of severity. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

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

Infections and infestations

Very common: bacterial infections, viral infections, [+]bronchitis.
Common: sepsis, [+]pneumonia, [+]febrile infection, [+]herpes zoster, [+]respiratory tract infection, fungal infections, infections of unknown origin, [+]acute bronchitis, [+]sinusitis, hepatitis B[1].
Rare: serious viral infection[2] including cytomegalovirus infection, herpes infection, hepatitis C and fulminant hepatitis, Pneumocystis jirovecii.
Very rare: progressive multifocal leukoencephalopathy (PML, see "Warnings and precautions").
Not known: neutropenic infection*, urinary tract infection*.

Blood and lymphatic system disorders

Very common: neutropenia (which may be prolonged and/or late in onset after completing a treatment cycle), leukopenia, [+]febrile neutropenia, [+]thrombocytopenia.
Common: anaemia, [+]pancytopenia, [+]granulocytopenia.

Uncommon: coagulation disorders, aplastic anaemia, haemolytic anaemia, lymphadenopathy.
Very rare: transient increase in serum IgM levels[3].
Not known: late neutropenia[3], haematotoxicity*.

Immune system disorders
Very common: infusion-related reactions[4], angioedema, decreased IgG levels.
Common: hypersensitivity.
Rare: anaphylaxis.
Very rare: tumour lysis syndrome, cytokine release syndrome[4], serum sickness.
Not known: infusion-related acute reversible thrombocytopenia[4].

Metabolism and nutrition disorders
Common: hyperuricaemia, hyperglycaemia, weight loss, peripheral oedema, face oedema, elevated LDH, hypocalcaemia.

Psychiatric disorders
Uncommon: depression, nervousness.

Nervous system disorders
Common: paraesthesia, hypoaesthesia, agitation, insomnia, vasodilatation, dizziness, anxiety.
Uncommon: dysgeusia.
Very rare: peripheral neuropathy, facial nerve palsy[5].
Not known: cranial neuropathy, sensory disturbances, loss of other senses[5].

Eye disorders
Common: lacrimation disorder, conjunctivitis.
Very rare: severe vision loss[5].

Ear and labyrinth disorders
Common: tinnitus, ear pain.
Not known: hearing loss[5].

Cardiac disorders
Common: [+]myocardial infarction[4, 6], arrhythmia, [+]atrial fibrillation, tachycardia, [+]cardiac disorder.
Uncommon: [+]left ventricular failure, [+]supraventricular tachycardia, [+]ventricular tachycardia, [+]angina, [+]myocardial ischaemia, bradycardia.
Rare: severe cardiac disorders[4, 6].

Very rare: heart failure[4, 6].

Vascular disorders

Common: hypertension, orthostatic hypotension, hypotension.

Very rare: vasculitis (predominantly cutaneous), leukocytoclastic vasculitis.

Respiratory, thoracic and mediastinal disorders

Common: bronchospasm[4], respiratory disease, chest pain, dyspnoea, increased cough, rhinitis.

Uncommon: asthma, bronchiolitis obliterans, lung disorder, hypoxia.

Rare: pulmonary oedema, interstitial lung disease[7].

Very rare: respiratory failure[4].

Not known: pulmonary infiltrates.

Gastrointestinal disorders

Very common: nausea.

Common: vomiting, diarrhoea, abdominal pain, dysphagia, stomatitis, constipation, dyspepsia, anorexia, throat irritation.

Uncommon: abdominal enlargement.

Very rare: gastrointestinal perforation or obstruction[7].

Hepatobiliary disorders

Very rare: hepatitis.

Skin and subcutaneous tissue disorders

Very common: pruritus, rash, [+]alopecia.

Common: urticaria, sweating, night sweats, [+]skin disorder.

Very rare: severe bullous skin reactions, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome)[7].

Musculoskeletal and connective tissue disorders

Common: hypertonia, myalgia, arthralgia, back pain, neck pain, pain.

Renal and urinary disorders

Very rare: renal failure (in association with tumour lysis syndrome)[4].

General disorders and administration site conditions

Very common: pyrexia, chills, asthenia, headache.

Common: tumour pain, tremor, flushing, malaise, cold symptoms, [+]fatigue, [+]shivering, [+]multiorgan failure[4], peripheral oedema, face oedema.
Uncommon: infusion site pain.

All grades (from mild to severe) were considered in calculating the frequencies of adverse reactions, except for adverse reactions marked with "+", where the frequency calculation was based only on severe reactions (≥grade 3 National Cancer Institute [NCI] common toxicity criteria). Only the highest frequency observed in a trial is listed.
[1] includes reactivation and primary infections; frequency based on R-FC regimen in relapsed/refractory CLL
[2] See also "Infections" section below
[3] See also "Haematological adverse reactions" section below
[4] See also "Infusion-related reactions" section below. Rare fatal cases were reported
[5] Signs and symptoms of cranial neuropathy. Occurred at various times up to several months after completion of MabThera therapy
[6] Observed mainly in patients with prior cardiac condition and/or cardiotoxic chemotherapy and were mostly associated with IRRs
[7] Includes fatal cases
* adverse events

Signs and symptoms suggestive of an IRR were reported in more than 50% of patients in clinical trials, and were predominantly seen during the first infusion, usually within the first two hours. These symptoms mainly comprised pyrexia, 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 symptoms of tumour lysis syndrome. Severe IRRs (such as bronchospasm or hypotension) occurred in up to 12% of cases.

Additional reactions reported in some cases were myocardial infarction, atrial fibrillation, pulmonary oedema and acute reversible thrombocytopenia. Exacerbations of pre-existing cardiac conditions such as angina pectoris or congestive heart failure or severe cardiac disorders (heart failure, myocardial infarction, atrial fibrillation), pulmonary oedema, multiorgan failure, tumour lysis syndrome, cytokine release syndrome, renal failure and respiratory failure were reported. The incidence of

infusion-related symptoms decreased substantially with subsequent infusions and was less than 1% after the eighth treatment cycle with MabThera.

Description of specific adverse reactions and additional information

Infections

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

Localised candida infections and herpes zoster were reported at a higher incidence in the MabThera-containing arm of randomised clinical studies. Severe infections occurred in about 4% of patients treated with MabThera monotherapy. Higher frequencies of infections overall, including grade 3 or 4 infections, were reported during MabThera maintenance treatment up to 2 years when compared to the observation group. There was no cumulative toxicity in terms of infections reported over the 2-year treatment period. In addition, other serious viral infections either new, reactivated or exacerbated, some of which were fatal, have been reported with MabThera treatment. The majority of patients received MabThera in combination with chemotherapy or as part of haematopoietic stem cell transplantation. Examples of these serious viral infections are infections caused by the herpes viruses (cytomegalovirus, varicella zoster virus and herpes simplex virus), JC virus (progressive multifocal leukoencephalopathy (PML)) and hepatitis C virus. Cases of fatal PML that occurred after disease progression and retreatment have also been reported in clinical trials. Cases of hepatitis B reactivation have been reported, the majority of which were in patients receiving MabThera in combination with cytotoxic chemotherapy. In patients with relapsed/refractory CLL, the incidence of grade 3/4 hepatitis B infection (reactivation and primary infection) was 2% with R-FC vs 0% with 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 usually in HIV-positive patients.

Haematological adverse reactions

In clinical trials with MabThera monotherapy given for 4 weeks, haematological abnormalities occurred in a minority of patients and were usually mild and reversible. Severe (grade 3/4) neutropenia was reported in 4.2%, anaemia in 1.1% and thrombocytopenia in 1.7% of the patients. During MabThera maintenance therapy for up to 2 years, leukopenia (5% vs 2%, grade 3/4) and neutropenia (10% vs 4%, grade 3/4) were reported at a higher incidence than in the observation group. The incidence of thrombocytopenia was low (<1%, grade 3/4) and was not different between treatment arms. During the treatment cycle in studies with MabThera in combination with chemotherapy, grade 3/4 leukopenia (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) and pancytopenia (R-FC 3% vs FC 1% in previously untreated CLL) were usually reported at higher frequencies compared to the chemotherapy group without MabThera. However, the higher incidence of neutropenia in patients treated with MabThera and chemotherapy was not associated with a higher incidence of infections and infestations compared to patients treated with chemotherapy alone. Studies in previously untreated and relapsed/refractory CLL have established that in up to 25% of patients treated with R-FC neutropenia was prolonged (defined as neutrophil count remaining below 1×10^9/l between day 24 and 42 after the last dose) or occurred with a late onset (defined as neutrophil count below 1×10^9/l later than 42 days after last dose in patients with no previous prolonged neutropenia or who recovered prior to day 42) following treatment with MabThera plus FC. There were no differences reported for the incidence of anaemia. Some cases of late neutropenia were reported more than 4 weeks after the last infusion of MabThera. In the CLL first-line study, Binet stage C patients experienced more adverse events in the R-FC arm than in the FC arm (R-FC 83% vs FC 71%). In the relapsed/refractory CLL study, grade 3/4 thrombocytopenia was reported in 11% of patients in the R-FC group and 9% of patients in the FC group.

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

Cardiovascular adverse reactions

Cardiovascular reactions during clinical trials with MabThera monotherapy were reported in 18.8% of patients with the most frequently reported events being hypotension and hypertension. Cases of grade 3 or 4 arrhythmia (including ventricular and supraventricular tachycardia) and angina pectoris during infusion were reported. During maintenance therapy, the incidence of grade 3/4 cardiac disorders in patients treated with MabThera was comparable to the observation group. Cardiac events were reported as serious adverse events (including atrial fibrillation, myocardial infarction, left ventricular failure, myocardial ischaemia) in 3% of patients treated with MabThera and <1% of patients in the observation group. In clinical 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%) than in the CHOP group (3 patients, 1.5%). All of these arrhythmias either occurred in the context of a MabThera infusion or were associated with predisposing conditions such as pyrexia, infection, acute myocardial infarction or pre-existing respiratory and cardiovascular disease. No differences between the R-CHOP and CHOP groups were observed in the incidence of other grade 3 and 4 cardiac events, including heart failure, myocardial disease and overt coronary artery disease. In

CLL, the overall incidence of grade 3 or 4 cardiac disorders was low both in the first-line study (4% R-FC, 3% FC) and in the relapsed/refractory study (4% R-FC, 4% FC).

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

Neurological disorders
During the treatment period (in the induction phase consisting of up to 8 cycles with R-CHOP), four patients (2%) in the R-CHOP group, all with cardiovascular risk factors, experienced thromboembolic cerebrovascular accidents during the first treatment cycle. There was no difference between the treatment groups in the incidence of other thromboembolic events. In contrast, three patients (1.5%) had cerebrovascular events in the CHOP group, all of which occurred during the follow-up period. In CLL, the overall incidence of grade 3 or 4 nervous system disorders was low both in the first-line study (4% R-FC, 4% FC) and in the relapsed/refractory study (3% R-FC, 3% FC).

Cases of posterior reversible encephalopathy syndrome (PRES)/reversible posterior leukoencephalopathy syndrome (RPLS) have been reported. Signs and symptoms included visual disturbance, headache, seizures and altered mental status, with or without associated hypertension. A diagnosis of PRES/RPLS requires confirmation by brain imaging. In the reported cases there were confirmed risk factors for PRES/RPLS, including the patient's 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. In the majority of these cases, MabThera was administered with chemotherapy.

IgG serum levels
In clinical trials evaluating MabThera as maintenance treatment in relapsed/refractory follicular lymphoma, median IgG serum levels were below the lower limit of normal (LLN) (<7 g/l) after induction treatment in both the observation and the MabThera groups. The median IgG serum level subsequently increased to values above the LLN in the observation group, but remained stable in the MabThera group. The proportion of patients with IgG serum levels below the LLN was about 60% in the MabThera group during the 2 year treatment period, while it decreased in the observation group (36% after 2 years).

A small number of spontaneous and literature cases of hypogammaglobulinaemia have been observed in children and adolescents treated with MabThera, in some cases severe and requiring long-term immunoglobulin substitution therapy. The consequences of long term B cell depletion in children and adolescents are unknown.

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

Patient subpopulations – MabThera monotherapy
Elderly patients (≥65 years):
The incidence of ADRs overall (all grades) was similar in elderly patients and younger patients (<65 years), as was also the case for grade 3/4 ADRs.

High tumour burden
Patients with high tumour burden had a higher incidence of grade 3/4 ADRs than those with low tumour burden (25.6% vs 15.4%). The incidence of ADRs of any grade was similar in these two groups.

Retreatment
The percentage of patients reporting ADRs on restarting treatment with MabThera was similar to the percentage in patients treated for the first time (any grade and grade 3/4 ADRs).

Patient subpopulation – MabThera combination therapy with CVP or CHOP chemotherapy
Elderly patients (≥65 years)
In previously untreated or relapsed/refractory CLL, the incidence of grade 3 and 4 blood and lymphatic adverse events was higher in elderly patients than in younger patients (<65 years).

Experience from clinical studies in paediatric patients with DLBCL/BL/BAL/BLL

A total of 309 paediatric patients received MabThera and were included in the safety analysis population.

The safety profile of MabThera in paediatric patients (≥6 months to <18 years old) with previously untreated advanced CD20-positive DLBCL/BL/BAL/BLL is generally consistent in type, nature and severity with the known safety profile in adult NHL and CLL patients. Addition of MabThera to

chemotherapy resulted in an increased risk of certain events such as infections (including sepsis) compared to chemotherapy alone *(see "Warnings and precautions")*.

Experience from clinical studies in adults with arthritis or ANCA-associated vasculitis

Frequenciesaredefinedasverycommon(≥1/10),common(≥1/100to<1/10),uncommon(≥1/1000to <1/100), rare(≥1/10,000to<1/1000)orveryrare(<1/10,000).

Long-term follow-up in adults:

In a long-term observational safety study, 97 adult patients with granulomatosis with polyangiitis/microscopic polyangiitis 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 safety profile was consistent with the well-established safety profile of MabThera in RA and granulomatosis with polyangiitis/microscopic polyangiitis, and no new adverse drug reactions were reported.

Infections and infestations

Very common: upper respiratory tract infection, urinary tract infection, infections (61.6%).

Common: pneumonia, bronchitis, sinusitis, gastroenteritis, tinea pedis.

Isolated cases of progressive multifocal leukoencephalopathy (PML), serum sickness-like reactions and reactivation of hepatitis B infection.

Blood and lymphatic system disorders

Very common: anaemia (16.2%), leukopenia (10.1%).

Events of neutropenia were observed with MabThera treatment, the majority of which were transient and mild or moderate in severity. Neutropenia can occur several months after the administration of MabThera.

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

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

In patients with ANCA-associated vasculitis, 24% of those in the MabThera group and 23% of those in the cyclophosphamide group developed grade 3 or greater neutropenia. The effect of multiple MabThera treatment cycles on the development of neutropenia in patients with ANCA-associated vasculitis has not been studied in clinical trials.

Immune system disorders *Very*

common: IRRs (12.1%). *Common*:

hypersensitivity reactions.

Uncommon: generalised oedema, bronchospasm, wheezing, laryngeal oedema, angioneurotic oedema, generalised pruritus, anaphylaxis, anaphylactoid reaction.

Rare: anaphylactic reactions, laryngeal oedema, angioedema.

Very rare: hypogammaglobulinaemia (IgM, IgG and/or IgA in lower normal range).

Metabolism and nutrition disorders

Common: hypercholesterolaemia, hot flushes.

Psychiatric disorders

Very common: insomnia (14.1%).

Common: depression, anxiety.

Nervous system disorders

Very common: headaches (17.2%).

Common: migraine, paraesthesia, dizziness, sciatica.

Vascular disorders

Very common: hypertension (12.1%).

Common: hypotension.

Respiratory, thoracic and mediastinal disorders

Very common: cough (13.1%), epistaxis (11.1%), dyspnoea (10.1%).

Rare: bronchospasm, wheezing.

Gastrointestinal disorders

Very common: nausea (18.2%), diarrhoea (17.2%).

Common: dyspepsia, upper abdominal pain, diarrhoea, gastro-oesophageal reflux, mouth ulcers.

Skin and subcutaneous tissue disorders

Very common: skin rash (10.1%).

Common: urticaria, alopecia.

Rare: pruritus.

Not known: toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS).

Musculoskeletal and connective tissue disorders

Very common: muscle spasms (17.2%), arthralgia (13.1%).

Common: muscle pain, osteoarthritis, bursitis.

General disorders and administration site conditions

Very common: peripheral oedema (16.2%), fatigue (13.1%).

Hepatobiliary disorders

Very common: elevated ALT levels (13.1%).

General

Common: asthenia, chills.

Experience from clinical studies in paediatric patients with severe active GPA or MPA

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 GPA or MPA.

Description of selected undesirable effects in paediatric patients

Infusion-related reactions (IRRs)

In the clinical trial in children and adolescents 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, rhinorrhoea and pyrexia (8%, for each symptom). The observed symptoms of IRRs 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 were reported. One serious grade 2 IRR (generalised oedema which resolved with treatment) was reported in one patient.

Infections

In the clinical trial in paediatric patients with severe active GPA and MPA, 91% of reported 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%) and 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 the paediatric clinical trial, no malignancies were reported with a follow-up period of up to 54 months.

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

Hypogammaglobulinaemia has been observed in paediatric patients treated with MabThera; some cases were severe, requiring long-term immunoglobulin replacement therapy. The consequences of long-term B lymphocyte deficiency in paediatric patients are unknown.
In the paediatric clinical trial, an event of hypogammaglobulinaemia was reported in 3/25 (12%) patients during the overall study period, 18 patients (72%) had prolonged (defined as Ig levels below lower limit of normal for at least 4 months) low IgG levels (of whom 15 patients also had prolonged low IgM). Three patients received treatment with intravenous immunoglobulin (IVIG). Based on limited data, no firm conclusions can be drawn regarding whether prolonged low IgG and IgM led to an increased risk of serious infection in these patients.

Immunogenicity
A total of 4/25 patients (16%) developed anti-drug antibodies (ADAs) to MabThera during the overall study period. Limited data show that there was no trend observed in the adverse reactions 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.

Experience from clinical studies in adults with pemphigus vulgaris

The safety profile of MabThera in PV patients was consistent with the known safety profile in other approved autoimmune indications (RA, GPA/MPA).

Tabulated list of adverse reactions
The ADRs presented in Table 3 include adverse events that occurred at a rate of ≥5% in MabThera-treated PV patients, with a ≥2% absolute difference in incidence between the MabThera-treated group

and the group treated with standard-dose prednisone up to month 24. No patients were withdrawn due to ADRs.

Table 3: 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 Herpes simplex 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 and connective tissue 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 in PV Study 1 included symptoms reported at the next scheduled visit after each infusion and adverse reactions occurring on the day of or one day after the infusion. The most common infusion-related reaction symptoms/preferred terms in PV Study 1 included headache, chills, high blood pressure, nausea, asthenia and pain.

The most common infusion-related reaction symptoms/preferred terms in PV Study 2 included dyspnoea, erythema, hyperhidrosis, flushing/hot flush, hypotension/low blood pressure and rash/rash pruritic.

Description of selected undesirable effects in adult patients with pemphigus vulgaris

Infusion-related reactions
In PV Study 1 (ML22196), infusion-related reactions were common (58%). Nearly all infusion-related reactions were mild to moderate. The proportion of patients experiencing infusion-related reactions was 29% (11 patients) after the first, infusion, 40% (15 patients) after the second infusion, 13% (5 patients) after the third infusion and 10% (4 patients) after the fourth infusion. No patients were withdrawn from treatment due to infusion-related reactions. Symptoms of infusion-related reactions were similar in type and severity to those seen in RA and GPA/MPA patients.

In PV Study 2 (WA29330), IRRs occurred primarily at the first infusion and the frequency of IRRs decreased with subsequent infusions: 17.9%, 4.5%, 3% and 3% of patients experienced IRRs after the first, second, third and fourth infusions, respectively. In 11/15 patients who experienced at least one IRR, the IRRs were grade 1 or 2. In 4/15 patients, grade ≥3 IRRs were reported and led to discontinuation of MabThera treatment; three of the four patients experienced serious (life-threatening) IRRs. Serious IRRs occurred at the first (2 patients) or second (1 patient) infusion and resolved with symptomatic treatment.

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

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

Laboratory abnormalities
In PV Study 2, a transient decrease in lymphocyte count, driven by a decrease in peripheral T cell populations, as well as a transient decrease in phosphorus level were very commonly observed post-

infusion in the MabThera arm. These were assumed to have been induced by intravenous infusion of the methylprednisolone premedication.

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

Undesirable effects after market launch

Immune system disorders

Very rare: severe IRRs with fatal outcome have been reported in post-marketing experience.

Hypogammaglobulinaemia (IgM, IgG or IgA below the normal range) has been observed in patients with RA and ANCA-associated vasculitis.

Skin and subcutaneous tissue disorders

Isolated cases of toxic-epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), some of which were fatal, have been reported in post-marketing experience.

Nervous system disorders

There have been post-marketing reports of cases of posterior reversible encephalopathy syndrome (PRES)/reversible posterior leukoencephalopathy syndrome (RPLS). Symptoms include visual disturbances, headache, seizures and altered mental state, with or without associated hypertension. The diagnosis of PRES/RPLS must be confirmed by brain imaging. In the reported cases there were recognised risk factors for PRES/RPLS, including hypertension, immunosuppressive therapy and/or other concomitant treatments.

Immunogenicity

In the clinical trials over 12-18 months, a total of 19/34 (56%) patients with PV who were treated with MabThera tested positive for ADA. The clinical relevance of ADA formation in MabThera-treated PV patients is unclear.

Reporting of suspected adverse reactions after marketing authorisation is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected new or serious adverse reaction via the ElViS (Electronic Vigilance System) online portal. Information can be found at www.swissmedic.ch.

Overdose

No experience with overdosage is available from clinical trials in humans. Single doses higher than 1000 mg have not been evaluated in controlled clinical studies.

The highest dose tested to date in patients with chronic lymphatic leukaemia was 5 g.

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

Treatment

In the event of overdosage the infusion should be stopped immediately and the patient closely monitored. In patients with B cell depletion the blood count should be checked regularly and attention paid to the increased risk of infection.

Properties/Effects

ATC code

L01XC02

Mechanism of action

Rituximab is a chimeric (mouse/human) monoclonal antibody that binds specifically to the transmembrane antigen CD20. This antigen is located on pre-B and mature B lymphocytes, but not on haematopoietic stem cells, pro-B cells, normal plasma cells or other normal tissue. The antigen is expressed on >95% of all cells of B cell non-Hodgkin's lymphomas (NHLs). Following antibody binding, CD20 is not internalised or shed from the cell membrane into the environment. CD20 does not circulate in the plasma as a free antigen and thus does not compete for antibody binding. Studies conducted to date have shown no connection between the intensity of CD20 expression on malignant cells and therapeutic response.

Rituximab binds to the CD20 antigen on B lymphocytes and causes B cell lysis. Possible mechanisms of cell lysis include complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC) and induction of apoptosis.

Pharmacodynamics

Peripheral B cell counts declined below normal following the first dose of MabThera. In patients treated for haematological malignancies, B cell recovery began within 6 months of completing therapy and generally returned to normal levels within 12 months after the end of treatment. In rheumatoid arthritis patients, the duration of B cell depletion was variable. The majority of patients received a further treatment before complete B cell repletion. In ANCA-associated vasculitis patients, peripheral blood

CD19 B cells declined after the first two infusions of MabThera to below 10 cells/µl and remained at this level in most patients for up to 6 months.

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

Of 1039 patients with rheumatoid arthritis tested for human antichimeric antibodies (HACA), 96 (9.2%) proved positive. The emergence of HACA in these patients was not associated with clinical deterioration or with an increased risk of reactions to subsequent infusions.

Out of 99 ANCA-associated vasculitis patients treated with MabThera, a total of 23 (23%) were HACA-positive after 18 months. The clinical relevance of HACA development in patients treated with MabThera is unclear.

Finally, *in vitro* studies have demonstrated that rituximab sensitises drug-resistant human B cell lymphoma lines to the cytotoxic effects of some chemotherapeutic agents.

Clinical efficacy

Follicular non-Hodgkin's lymphoma in adult patients

Monotherapy

In the pivotal study, 166 patients with relapsed or chemoresistant low-grade or follicular B cell NHL received 375 mg/m^2 of MabThera as an intravenous infusion once weekly for 4 weeks. The overall response rate (ORR) in the intent-to-treat (ITT) population was 48% (95% confidence interval [$CI_{95\%}$] 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 International Working Formulation (IWF) B, C and D histological subtypes compared to the IWF A subtype (58% vs 12%), higher in patients whose largest lesion was <5 cm in diameter than in those with diameters >7 cm (53% vs 38%), and higher in patients with chemosensitive relapse compared to those with chemoresistant relapse (defined as duration of response <3 months; 50% vs 22%). The ORR in patients with a previous autologous bone marrow transplant (ABMT) was 78% vs 43% in those without. Neither age, sex, lymphoma grade, initial diagnosis, presence or absence of a high tumour burden, normal or elevated LDH nor the presence of extranodal disease had a statistically significant effect on response to MabThera.

Combination with CVP

In a randomised open study a total of 321 previously untreated patients with low-grade or follicular B cell non-Hodgkin's lymphoma received CVP chemotherapy (cyclophosphamide 750 mg/m² body surface area vincristine 1.4 mg/m² body surface area up to a maximum of 2 mg on day 1 and prednisolone 40 mg/m² body surface area/day on days 1-5) every 3 weeks for 8 treatment cycles or MabThera 375

mg/m² body surface area in combination with CVP (R-CVP). MabThera was administered on day 1 of each treatment cycle. R-CVP led to significant benefit over CVP in terms of the primary endpoint (time to "treatment failure", defined as progression, relapse after response, institution of new lymphoma therapy, no response after 4 cycles, death: 25.9 months versus 6.7 months, p<0.0001).

Induction therapy and subsequent maintenance therapy in previously untreated patients

In a prospective open international phase III multicentre study, 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 investigating physician's choice. In total, 1078 responded to the induction therapy (ORR 99%); of these, 1018 were randomised and allocated to MabThera maintenance therapy (n=505) or observation (n=513).

The two treatment groups were well balanced in baseline characteristics and disease status. MabThera maintenance therapy consisted of a single infusion of MabThera 375 mg/m^2 body surface area every 2 months until disease progression or for a maximum of 2 years.

After a median 25 months' follow-up from randomisation, MabThera maintenance therapy in patients with previously untreated follicular NHL achieved clinically relevant and statistically significant improvement in the primary endpoint – investigator evaluation of progression-free survival (PFS) – versus patients without maintenance therapy. This improvement in PFS was confirmed by an independent review committee (IRC).

The significant benefit of MabThera maintenance therapy was also observed in the secondary endpoints of event-free survival (EFS) and overall response rate (ORR) (see Tables 4 and 5 below).

Table 4: Overview of efficacy results for maintenance MabThera vs observation (at 2 years)

	Observation	**Rituximab**	**HR (95% CI)**	**p value**
At 2 years	N=513	N=505		
median PFS	NR	NR	0.50 (0.39, 0.64)	<0.0001
median EFS	37.8 months	NR	0.54 (0.43, 0.69)	<0.0001
median OS	NR	NR	0.89 (0.45, 1.74)	0.725
ORR	219/398 (55%)	288/389 (74%)	_	<0.00015

NR: not reached at time of clinical cut-off

Table 5: Overview of efficacy results for maintenance MabThera vs observation (at 6 years)

	Observation	Rituximab	HR (95% CI)	p value
At 6 years	N=513	N=505		
median PFS	49 months	NR	0.58 (0.48. 0.69)	<0.0001
median EFS	48 months	NR	0.61 (0.51, 0.72)	<0.0001
median OS	NR	NR	1.02 (0.71, 1.47)	0.896
ORR	309/509 (61%)	395/500 (74%)	_	<0.0001

NR: not reached at time of clinical cut-off

The benefit of MabThera maintenance treatment was confirmed across all study subgroups including sex (male, female), age (<60 years, ≥60 years), FLIPI score (1, 2 or 3) and induction treatment (R-CHOP, R-CVP or R-FCM), regardless of the quality of response to induction treatment (CR or PR).

Induction and maintenance treatment in patients with relapsed or refractory disease

In an open, international, prospective multicentre phase III study, 465 patients with relapsed/treatment-resistant follicular NHL were randomised in a first phase to induction treatment with six cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone; N=231) or MabThera plus CHOP (R-CHOP, N=234). The two treatment groups were well balanced in baseline characteristics and disease status. In total, 334 patients who had achieved complete or partial remission after induction therapy were randomised in a second phase to MabThera maintenance therapy (N=167) or follow-up (N=167). MabThera maintenance therapy consisted of a single infusion of MabThera 375 mg/m^2 body surface area every 3 months until disease progression or for a maximum of 2 years.

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

Table 6: Induction phase (31 months median follow-up)

	CHOP	R-CHOP	p value
Primary efficacy parameters			
ORR	74%	87%	0.0003
CR	16%	29%	0.0005
PR	58%	58%	0.9449
Secondary efficacy parameters			
OS (median)	NR	NR	0.0508
PFS (median)	19.4 months	33.2 months	0.0001

NR = not reached; ORR = overall response rate; CR = complete response; PR = partial response; OS = overall survival; PFS = progression-free survival

Median follow-up for patients randomised in the maintenance phase of the study was 28 months. MabThera maintenance therapy caused a clinically relevant and statistically significant improvement of the primary endpoint, progression-free survival (PFS: time from maintenance phase randomisation to relapse, disease progression or patient death), compared to follow-up alone (p<0.0001, log-rank test). Median PFS in the MabThera group was 42.2 months vs 14.3 months in the follow-up group. Cox regression analysis showed that MabThera maintenance therapy reduced the risk of disease progression or patient death by 61% compared to follow-up (95% CI: 45%-72%). Kaplan-Meier-estimated PFS rates after 12 months were 78% with MabThera maintenance therapy compared to 57% in the follow-up group. Analysis of overall survival confirmed the significant benefit of MabThera maintenance therapy over follow-up (p=0.0039, log-rank test). MabThera maintenance therapy reduced the risk of death by 56% (95% CI: 22%-75%).

Median time to new lymphoma therapy was significantly longer with MabThera maintenance therapy than with follow-up alone (38.8 months vs 20.1 months, p<0.0001, log-rank test). The risk of having to institute new treatment was halved (95% CI: 30%-64%). In patients with complete response or unconfirmed complete response (CR/CRu) as their best response to induction therapy, MabThera maintenance therapy significantly prolonged median disease-free survival (DFS) compared to follow-up (53.7 months vs 16.5 months, p=0.0003, log-rank test) (see Table 7 below). The risk of relapse in CR patients was reduced by 67% (95% CI: 39%-82%).

Table 7: Maintenance phase (28 months median follow-up)

Efficacy parameters	Kaplan-Meier estimate of median time to event (months)		
	Follow-up (N=167)	MabThera (N=167)	Log-rank p value
Progression-free survival (PFS)	14.3	42.2	<0.0001
Overall survival	NR	NR	0.0039
Time to new lymphoma therapy	20.1	38.8	<0.0001
Disease-free survival[a]	16.5	53.7	0.0003

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

Diffuse large B cell non-Hodgkin's lymphoma in adult patients

In a randomised open study a total of 399 previously untreated elderly patients (aged 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 prednisone 40 mg/m^2/day on days 1-5) every 3 weeks for eight treatment cycles, or MabThera 375 mg/m^2 plus CHOP (R-CHOP). MabThera was administered on day 1 of the treatment cycle. Efficacy was analysed in all randomised patients (CHOP: N=197; R-CHOP: N=202) over a (median) follow-up of approximately

31 months. The two treatment groups were well balanced in baseline characteristics and disease status. The final analysis confirmed that R-CHOP significantly prolonged (p=0.0001) the duration of the primary efficacy endpoint, event-free survival (events: death, relapse, lymphoma progression or institution of new lymphoma treatment). Kaplan-Meier estimates of median event-free survival were 35 months in the R-CHOP treatment group compared to 13 months in the CHOP treatment group. This was equivalent to a risk reduction of 41%. At 24 months, estimates for overall survival were 68.2% in the R- CHOP group compared to 57.4% in the CHOP group. Subsequent analysis at 60 months confirmed the benefit of R-CHOP over CHOP: the overall survival rate after R-CHOP was 62.4% compared with 50.8% in the CHOP group (p=0.0071), representing a survival risk reduction of 32%.

Analysis of all secondary endpoints (response rates, PFS, DFS, duration of response) confirmed the benefit of R-CHOP treatment over CHOP. The CR rate after treatment cycle 8 was 76.2% in the R-CHOP group compared to 62.4% in the CHOP group (p=0.0028). The risk of disease progression was reduced by 46% and the risk of relapse by 51%.

In all patient subgroups (sex, age, age-adjusted International Prognostic Index [IPI], Ann Arbor stage, Eastern Cooperative Oncology Group [ECOG], β2-microglobulin, LDH, albumin, B symptoms, high tumour burden, extranodal sites, bone marrow involvement), the risk ratios for event-free survival and overall survival (R-CHOP vs CHOP) were less than 0.83 and 0.95. R-CHOP treatment correlated with improved outcome for both high- and low-risk patients according to age-adjusted IPI.

Chronic lymphocytic leukaemia (CLL) in adult patients

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 in the first cycle at a dosage of 375 mg/m^2 one day before chemotherapy and at a dosage of 500 mg/m^2 on day 1 of each subsequent treatment cycle.

In the first-line study, median progression-free survival (primary endpoint) was 42.8 months in the R-FC group and 32.5 months in the FC group (p<0.0001). The analysis of overall survival showed a survival advantage in the R-FC arm (p=0.0427).

The overall response rate was 86.1% vs 72.7%, with complete response (CR) in 36.0% vs 17.2% (p<0.0001).

In the relapsed/refractory disease study, 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). Median overall survival has not yet been reached in the R-FC arm and is 51.9 months in the FC arm.

The overall response rate was 69.9% vs 58.0%, with complete response (CR) in 24.3% vs 13.0% (p<0.0007).

CD20-positive DLBCL/BL/BAL/BLL in paediatric patients

A multicentre, open-label, randomised 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 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 of the adult normal values (>N×2)] or any stage IV or BAL. Patients were randomised to receive either LMB chemotherapy or six intravenous infusions of MabThera at a dose of 375 mg/m² BSA in combination with LMB chemotherapy (two during each of the two induction phases and one during each of the two consolidation phases) as per the LMB regimen.
A total of 328 randomised patients in two treatment arms – LMB (LMB chemotherapy) and R-LMB (LMB chemotherapy plus MabThera) – were included in the efficacy analyses, one patient under 3 years of age receiving MabThera in combination with LMB chemotherapy.

The two treatment arms, LMB (LMB chemotherapy) and R-LMB (LMB chemotherapy with MabThera), were well balanced in baseline characteristics. Patients had a median age of 7 and 8 years in the LMB arm and R-LMB arm, respectively. Approximately half of patients 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 had 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 half of the 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 event-free survival (EFS), where an event was defined as occurrence of progressive disease, relapse, second malignancy, death from any cause, or non-response as evidenced by detection of viable cells in residue after the second CYVE phase, whichever occurs first. The secondary efficacy endpoints were OS and CR (complete remission).

At the prespecified interim analysis with a median follow-up of approximately 1 year, clinically relevant improvement was observed in the primary endpoint of EFS, with 1-year 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 of 0.33 (95% CI, 0.14-0.79). On the independent data monitoring committee (IDMC) recommendation based on this result, randomisation was halted and patients in the LMB arm were allowed to cross over to the MabThera arm.

Primary efficacy analyses were performed in 328 randomised patients (ITT population) with a median follow-up of 3.1 years. The primary efficacy analysis showed an EFS benefit for MabThera in addition to LMB chemotherapy over LMB chemotherapy alone. The 3-year EFS rates were 82.3% (95% CI: 75.7%, 87.5%) for chemotherapy alone (LMB arm; N=164) with 28 events and 93.9% (95% CI: 89.1%, 96.7%) for MabThera plus chemotherapy (R-LMB arm; N=164) with 10 events; the adjusted Cox HR was 0.32 (90% CI: 0.17, 0.58) with a one-sided log-rank test p-value of 0.0006. The Cox regression analysis was adjusted for national group, histology and treatment group.
At the time of the primary efficacy analyses, the results for the secondary endpoint of overall survival (OS) were as follows: the 3-year OS rates in the LMB and R-LMB treatment arms were 87.3% (95% CI: 81.2%, 91.6%) and 95.1% (95% CI: 90.5%, 97.5%), respectively, with 20 deaths recorded in the LMB arm and 8 deaths in the R-LMB arm (adjusted Cox HR: 0.36 [95% CI: 0.16-0.81]).

Rheumatoid arthritis

The efficacy and safety of MabThera in the treatment of rheumatoid arthritis were demonstrated in three randomised, controlled, double-blind, multicentre studies.

Study 1 (WA17042) was a phase III double-blind comparative study with 517 patients who had failed to respond adequately to, or had not tolerated, one or more treatments with TNF inhibitors. In order to be included in the study, patients had to suffer from severe active rheumatoid arthritis that had been diagnosed in accordance with the criteria of the American College of Rheumatology (ACR). The primary endpoint was the percentage of patients who had achieved an ACR20 response after 24 weeks. On two occasions separated by an interval of 15 days the patients received an i.v. infusion of 1000 mg MabThera, in each case after infusion of 100 mg methylprednisolone. All patients also received oral methotrexate (10-25 mg/week) plus oral prednisone 60 mg from day 2 to day 7 and 30 mg from day 8 to day 14 after the first infusion.

Patients were followed beyond week 24 for long-term endpoints, including radiographic assessment at 56 weeks. During this time patients may have received further courses of MabThera under an open-label extension study protocol.

Study 2 (WA17043) was a randomised, controlled, double-blind, multifactorial (3 × 3), double-dummy phase II study comparing two dosage levels of rituximab (2 × 1000 mg and 2 × 500 mg). MabThera was administered with or without infused glucocorticoid therapy (one of two therapeutic schemes) in combination with weekly methotrexate administration to patients who suffered from active rheumatoid arthritis and had failed to respond to treatment with at least 1-5 DMARDs other than methotrexate.

Study 3 (WA16291) was a controlled, double-blind, double-dummy study assessing MabThera as a single agent and in combination with cyclophosphamide or methotrexate in patients with active rheumatoid arthritis who had failed to respond to treatment with one or more DMARDs.

Patients given weekly methotrexate (10-25 mg per week) served as a comparator group in all three studies.

Effect on disease activity

In all three studies, treatment with 2 × 1000 mg rituximab resulted in a significant increase in the proportion of patients who experienced an improvement of at least 20% in their ACR value compared to treatment with methotrexate alone (see Table 8 below). The therapeutic effect was similar in all patients and was independent of rheumatoid factor status, age, sex, body surface area, race, number of previous treatments and disease status.

A clinically and statistically significant improvement was also found in all the individual components of the ACR response (tender and swollen joints, global assessment by patient and physician, HAQ Disability Index score, pain assessment and C-reactive protein [mg/dl]).

Table 8: ACR response rates after 24 weeks in the various studies (ITT population)

	ACR response	**Placebo + MTX**	**Rituximab + MTX 2 × 1000 mg**	**Rituximab + MTX 2 × 500 mg**
Study 1 (WA17042) [1]		N=201 RF-positive and -negative patients	N=298 RF-positive and -negative patients	–
	ACR20 ACR50 ACR70	36 (18%) 11 (5%) 3 (1%)	153 (51%)[3] 80 (27%)[3] 37 (12%)[3]	– – –
Study 2 (WA17043) [2]		N=143 RF-positive and -negative patients	N=185 RF-positive and -negative patients	N=123 RF-positive patients
	ACR20 ACR50 ACR70	45 (31%) 19 (13%) 6 (4%)	96 (52%)[4] 61 (33%)[4] 28 (15%)[4]	68 (55%)[4] 40 (33%)[4] 16 (13%)[5]
Study 3 (WA16291) [2]		N=40 RF-positive patients	N=40 RF-positive patients	–
	ACR20 ACR50 ACR70	15 (38%) 5 (13%) 2 (5%)	28 (70%)[5] 17 (43%)[5] 9 (23%)[5]	– – –

[1] Inadequate response to TNF inhibitors

[2] Inadequate response to one or more DMARDs

[3] $p \leq 0.0001$; [4] $p \leq 0.001$; [5] $p<0.05$

RF = rheumatoid factor

In Study 3 (WA16291) the efficacy of MabThera as a single agent was assessed in an additional treatment arm. This showed an ACR20 response rate of 65% compared to 38% with methotrexate alone (p=0.025).

The 28-joint Disease Activity Score (DAS28) fell significantly more in the patients treated with MabThera than in those treated with methotrexate alone. Significantly more patients achieved a moderate to good European League Against Rheumatism (EULAR) response with MabThera than with methotrexate alone (see Table 9 below).

Table 9: Comparison of DAS and EULAR response rates after 24 weeks in the various studies (ITT population)

	Placebo + MTX	**Rituximab + MTX 2 × 1000 mg**	**Rituximab + MTX 2 × 500 mg**
Study 1 (WA17042)[1]	N=201 RF-positive and -negative patients	N=298 RF-positive and -negative patients	–
DAS28 change [mean (standard deviation)]	-0.4 (1.2)	-1.9 (1.6)*	–
EULAR response (%)			–
None	78%	35%	–
Moderate	20%	50%*	–
Good	2%	15%	–
Study 2 (WA17043)[2]	N=143 RF-positive and -negative patients	N=185 RF-positive and -negative patients	N=123 RF-positive patients
DAS28 change [mean (standard deviation)]	-0.8 (1.4)	-2.0 (1.6)	-1.9 (1.4)
EULAR response			–
None	61%	37%	28%
Moderate	35%	40%	59%
Good	4%	23%	14%
Study 3 (WA16291)[2]	N=40 RF-positive patients	N=40 RF-positive patients	–
DAS change [mean (standard deviation)]	-1.3 (1.2)	-2.6 (1.3)	–
EULAR response			–
None	50%	18%	–
Moderate	45%	63%	–
Good	5%	20%	–

[1] Inadequate response to TNF inhibitors

[2] Inadequate response to one or more DMARDs

* p<0.0001; p values for studies 2 and 3 not calculated

RF = rheumatoid factor

Radiographic response

Study WA17042 conducted in TNF-IR patients receiving MabThera in combination with methotrexate demonstrated significantly less radiographic progression at 56 weeks in the patients in the MabThera + methotrexate group than in patients in the group receiving methotrexate alone. A higher proportion of patients receiving MabThera also had no erosive progression over 56 weeks (see Table 10 below).

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

Table 10: Radiographic outcomes at 1 year in study WA17042 (MITT population)

	Placebo + MTX	**Rituximab + MTX (2 × 1000 mg)**
Study WA17042 (TNF-IR)	**N=184**	**N=273**
Mean change from baseline:		
Modified total Sharp score	2.31	1.00
Erosion score	1.32	0.59
Joint space narrowing score	0.99	0.41
Proportion of patients with no radiographic change	46%	53%
Proportion of patients with no erosive change	52%	61%

Effect on quality of life

The patients treated with MabThera reported an improvement in all patient-related results (HAQ-DI, FACIT-F and SF-36 questionnaires, see Tables 11 and 12 below). Compared to the patients treated with methotrexate alone, the patients treated with MabThera showed a significant reduction in the disability (HAQ-DI) and fatigue (FACIT-F) indexes and an improvement in the physical health and mental health categories of the SF-36 questionnaire.

Table 11: Short Form Health Survey (SF-36): mean and categorical change from baseline to week 24

	Study 1 (WA17042)	**Study 2 (WA17043)**

	Placebo + MTX N=197	Rituximab + MTX N=294	Placebo + MTX N=141	Rituximab + MTX N=178
Mental health				
Mean change (standard deviation)	1.3 (9.4)	4.7 (11.8)	1.8 (8.0)	3.2 (11.2)
p value*		0.0002		
Improved	40 (20%)	111 (38%)	29 (21%)	60 (34%)
Unchanged	128 (65%)	144 (49%)	99 (70%)	90 (51%)
Worsened	29 (15%)	39 (13%)	13 (9%)	28 (16%)
p value*		0.0015		
Physical health				
Mean change (standard deviation)	0.9 (5.7)	5.8 (8.5)	1.96 (6.3)	6.1 (8.2)
p value*		<0.0001		
Improved	25 (13%)	141 (48%)	37 (26%)	88 (49%)
Unchanged	158 (80%)	136 (46%)	92 (65%)	81 (46%)
Worsened	14 (7%)	17 (6%)	12 (9%)	9 (5%)
p value*		<0.0001		

* The data from Study 2 (WA17043) were not analysed.

Mental health change category: change >6.33 = improved,

-6.33 ≤change <6.33 = unchanged, change <-6.33 = worsened.

Physical health change category: change >5.42 = improved,

-5.42 ≤change <5.42 = unchanged, change <-5.42 = worsened.

Table 12: HAQ and FACIT-F response at week 24 in Study 1 (WA17042)

Response at week 24: Change from baseline value	Placebo + MTX[1] N=201 Mean (standard deviation)	Rituximab + MTX[1] N=298 Mean (standard deviation)	p value
HAQ[2]	-0.1 (0.5)	-0.4 (0.6)	<0.0001
FACIT-F[3]	-0.5 (9.8)	-9.1 (11.3)	<0.0001

[1] methotrexate

[2] Health Assessment Questionnaire (HAQ)

[3] Functional Assessment of Chronic Illness Therapy (FACIT-F)

At 24 weeks the proportion of patients in all three studies achieving clinically significant improvement in HAQ-DI index (defined as a decrease >0.25 in individual total score) was greater with MabThera than with methotrexate alone.

Laboratory values

Approximately 10% of patients with rheumatoid arthritis tested positive for HACA in clinical studies. The emergence of HACA in these patients was not associated with clinical deterioration or with an increased risk of reactions to subsequent infusions. The presence of HACA may be associated with worsening of IRRs or allergic reactions after the second infusion of subsequent courses. Failure to deplete B cells after further treatment courses has been observed rarely.

In one of the studies, 15 of 308 patients (4.8%) treated with rituximab and 8 of 209 patients (3.8%) treated with methotrexate alone tested negative for antinuclear antibodies (ANA) on day 1 and positive at week 16 and/or week 24. The profile of adverse events in these patients provided no evidence of incident autoimmune disease.

In rheumatoid factor (RF)-positive patients a marked decrease (range: 45%-64%) in RF concentrations was observed in all three studies after rituximab treatment.

The total plasma immunoglobulin concentration, total lymphocyte count and leukocyte count generally remained within normal limits after treatment with MabThera apart from a transient fall in leukocyte count in the first 4 weeks after treatment. Titres of antigen-specific IgG antibodies against mumps, rubella, varicella, tetanus toxoid, influenza and Streptococcus pneumoniae remained stable for 24 weeks in patients with rheumatoid arthritis after treatment with MabThera.

The effect of MabThera on various biomarkers was studied in patients included in Study 3 (WA16291). This substudy examined the effect of a single treatment cycle of MabThera on biochemical marker concentrations. These included inflammatory markers (interleukin-6, C-reactive protein, serum amyloid A protein and S100 protein isotypes A8 and A9), autoantibodies (RF and anticyclic citrullinated peptide), immunoglobulin production and bone turnover (osteocalcin and type 1 collagen N-terminal propeptide [P1NP]). Treatment with MabThera – as both monotherapy and combination therapy with methotrexate or cyclophosphamide – significantly decreased inflammatory marker concentrations in the first 24 weeks of follow-up compared to methotrexate alone. The concentration of bone turnover markers osteocalcin and P1NP increased significantly in the groups taking MabThera compared to methotrexate alone.

Study with a shortened infusion time of 2 hours for the second and subsequent infusions

In a multicentre, open-label, single-arm trial, 351 patients with moderate to severe active RA who had responded inadequately to at least one tumour necrosis factor inhibitor and were treated with methotrexate received 2 cycles of MabThera treatment. MabThera-naïve patients (n=306) and those who had already received treatment with MabThera (n=45) were eligible to participate in the trial.

Patients received 2 cycles of MabThera 2 × 1000 mg + methotrexate, with the first cycle administered on days 1 and 15 and the second cycle six months later on days 168 and 182. The first infusion of the first cycle (day 1 infusion) was administered over a 4.25-hour period (255 minutes). The second infusion of the first cycle (day 15 infusion) and both infusions in the second cycle (day 168 and day 182 infusions) were administered over a period of 2 hours. Patients experiencing a serious infusion-related reaction (IRR) with an infusion were excluded from the study.

The primary objective of the study was to assess the safety of administering the second infusion (day 15 infusion) over a period of 2 hours (120 minutes).

The incidence, type and severity of IRRs were consistent with those already observed in the past with prolonged infusions. No serious IRRs were observed. A direct comparison with infusion over 3 hours 15 minutes is not available. Of the 337 patients given the infusion on study day 15, however, 10 patients who had not shown a reaction with the first infusion experienced grade 1 or 2 IRRs (erythema, chills, nausea, headache, paraesthesia) with the day 15 infusion. One of these patients discontinued the study because of the IRR (grade 2 urticaria).

Severe active ANCA-associated vasculitis (GPA/MPA) in adult patients

A total of 197 patients with severe active ANCA-associated vasculitis (AAV) were enrolled and treated in an active-controlled, randomised, double-blind, multicentre non-inferiority study. The patients were 15 years of age or older and had been diagnosed with either severe active granulomatosis with polyangiitis, also known as Wegener's granulomatosis (75% of patients) or microscopic polyangiitis (24% of patients) according to the criteria of the Chapel Hill consensus conference (in 1% of patients the type of ANCA-associated vasculitis was unknown).

Patients were randomised in a 1:1 ratio to receive treatment with either oral cyclophosphamide (2 mg/kg body weight/day) for 3 to 6 months followed by azathioprine or MabThera (375 mg/m^2) once weekly for 4 weeks. In both treatment arms, patients received intravenous pulse therapy with methylprednisolone 1000 mg daily (or another glucocorticoid at an equivalent dose) for 1 to 3 days followed by oral prednisone (1 mg/kg body weight/day, not exceeding 80 mg/day). The prednisone had to have been tapered to zero within 6 months of starting the study treatment.

The primary endpoint was the achievement of complete remission after 6 months, defined by a Birmingham Vasculitis Activity Score for Wegener's granulomatosis (BVAS/WG) of 0 and the discontinuation of glucocorticoid therapy. The predefined non-inferiority margin for the difference between treatments was 20%. The study showed at least equivalent efficacy (non-inferiority) by MabThera compared to cyclophosphamide with respect to complete remission after 6 months (see Table 13 below). In addition, on the basis of historical control data, the complete remission rate in the MabThera treatment arm was significantly higher than the estimated complete remission rate in patients with severe ANCA-associated vasculitis who were untreated or treated with glucocorticoids only.

Efficacy was observed both in patients with newly diagnosed ANCA-associated vasculitis and in patients with recurrent disease.

Table 13: Percentage of patients achieving complete remission after 6 months (intent-to-treat population)

	MabThera (N=99)	**Cyclophosphamide (N=98)**	**Treatment difference (MabThera – cyclophosphamide)**
Rate	63.6%	53.1%	10.6%
95.1% CI	(54.1%, 73.2%)	(43.1%, 63.0%)	(-3.2%, 24.3%)

In the RAVE study, patients in the MabThera treatment group received no maintenance therapy whereas those in the cyclophosphamide group received azathioprine maintenance therapy after the induction of remission. Maintenance of efficacy in the RAVE study was assessed after 12 and 18 months; the most important secondary endpoints of the study were complete remission after 12 and 18 months. In the MabThera group 44% of patients were in complete remission after 6 and 12 months and 38% after 6, 12 and 18 months. Of the patients treated with cyclophosphamide (followed by azathioprine), 38% were in complete remission after 6 and 12 months and 31% after 6, 12 and 18 months.

Severe active ANCA-associated vasculitis (GPA/MPA) in paediatric patients

Study WA25615 (PePRS) was a multicentre, open-label, single-arm, uncontrolled study in 25 paediatric patients with severe active GPA or MPA. The median age of patients in this study was 14 years (range: 6-17 years) and the majority of patients (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 of an 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 received a minimum of 3 doses of i.v. methylprednisolone (30 mg/kg/day, not exceeding 1 g/day) prior to the first MabThera i.v. infusion. If clinically indicated, additional daily doses (up to three) of i.v. methylprednisolone could be given. The remission induction regimen consisted of four once-weekly i.v. infusions of MabThera at a dose of 375 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 (max. 10 mg/day) by month 6. After the remission induction phase, patients could, at the discretion of the investigator, receive

subsequent MabThera infusions on or after month 6 to maintain remission as assessed by the Paediatric Vasculitis Activity Score (PVAS) and to control disease activity (including progressive disease or flare) or achieve first remission.

All 25 patients received all i.v. infusions of the 6-month remission induction phase. A total of 24 out of 25 patients completed at least 18 months of follow-up.

The aim of this study was to evaluate safety, PK parameters and efficacy of MabThera in paediatric GPA and MPA patients (≥2 to <18 years old). The efficacy analysis was exploratory and assessed using the Paediatric Vasculitis Activity Score (PVAS) (Table 14).

Cumulative glucocorticoid dose (i.v. and oral) by month 6:
In study WA25615, 24 of 25 patients (96%) achieved oral glucocorticoid taper to 0.2 mg/kg/day (maximum 10 mg/day) by month 6 in accordance with the protocol-defined oral glucocorticoid tapering regimen.

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 month 18 (median = 5 mg [IQR: 1-5]).

Follow-up treatment
Follow-up treatment was not specifically defined in the study, but was conducted according to clinical judgment and at the investigator's discretion, and is correspondingly heterogeneous.

Table 14: 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$^{\alpha}$
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 (maximum 10 mg/day) 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/m² × 4 infusions) up to month 6 was identical for all patients. Follow-up treatment after month 6 was at the investigator's discretion.

Pemphigus vulgaris in adults

PV Study 1 (study ML22196)

The efficacy and safety of MabThera in combination with short-term, low-dose glucocorticoid (prednisone) therapy were evaluated in patients with newly diagnosed moderate to severe pemphigus (74 pemphigus vulgaris [PV] and 16 pemphigus foliaceus [PF]) in this randomised, open-label, controlled, multicentre study.

Patients were between 19 and 79 years of age and had not received prior treatment for pemphigus. In the PV population, 5 (13%) patients in the MabThera group and 3 (8%) patients in the standard-dose 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 as 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 over 3 months if they had moderate disease or 1 mg/kg/day oral prednisone tapered over 6 months if they had severe disease. The second intravenous infusion of 1000 mg MabThera was given on study day 15. Maintenance infusions of 500 mg MabThera were administered at months 12 and 18. Patients randomised to the standard-dose prednisone group received an initial dose of 1 mg/kg/day oral prednisone tapered over 12 months if they had moderate disease or 1.5 mg/kg/day oral prednisone tapered over 18 months if they had severe disease. Patients in the MabThera group who relapsed could receive an additional infusion of 1000 mg MabThera in combination with a reintroduced or escalated prednisone dose. Maintenance and relapse infusions were administered no sooner than 16 weeks after the previous infusion.

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

PV Study 1 results

The study showed statistically significant superiority of MabThera and low-dose prednisone over standard-dose prednisone in achieving CRoff ≥2 months at month 24 in PV patients (see Table 15).

Table 15: Percentage of PV patients who achieved complete remission off corticosteroid therapy for two months or more at month 24 (intent-to-treat population – PV)

	Rituximab + Prednisone n=38	Prednisone n=36	p-value[a]	95% CI[b]
Number of responders (response rate [%])	34 (89.5%)	10 (27.8%)	<0.0001	61.7% (38.4, 76.5)

[a] p-value is from Fisher's exact test with mid-p correction

[b] 95% confidence interval is corrected Newcombe interval

PV Study 2 (study WA29330)

In a randomised, double-blind, double-dummy, active comparator, multicentre 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. Patients had a confirmed diagnosis of PV within the previous 24 months and evidence of moderate to severe disease (defined as a total Pemphigus Disease Area Index [PDAI] activity score of ≥15).

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

The primary efficacy objective of this study was to evaluate at week 52 the efficacy of MabThera compared with MMF in achieving sustained complete remission, defined as healing of lesions with no new active lesions (i.e. PDAI activity score of 0) without use of corticosteroids and maintenance of this response for at least 16 consecutive weeks during the 52-week treatment period.

PV Study 2 results

The study demonstrated the superiority of MabThera over MMF in combination with a tapering course of oral corticosteroids in achieving complete remission off corticosteroids for ≥16 weeks at week 52 in PV patients (Table 16). The majority of patients in the mITT population were newly diagnosed (74%) and 26% of patients had established disease and corresponding prior treatment (duration of illness ≥6 months).

Table 16: Percentage of PV patients who achieved sustained complete remission off corticosteroid therapy for ≥16 weeks week 52 (modified intent-to-treat population)

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

Pharmacokinetics

Absorption

MabThera is administered intravenously.

Distribution

The mean C_{max} following the fourth infusion of 375 mg/m^2 was 486 µg/ml (range 77.5 to 996.6 µg/ml). Following the intravenous administration of 500 and 1000 mg doses of MabThera on two occasions two weeks apart, mean C_{max} values were 183 µg/ml (range 81.8 to 279 µg/ml) and 370 µg/ml (range 212 to 637 µg/ml) respectively.

The mean steady-state distribution volume was approximately 4.6 l (range 1.7 to 7.51 l).

Metabolism

Like all proteins, rituximab is broken down in the liver.

Elimination

The estimated mean terminal elimination half-life of rituximab is 20.8 to 24 days (range 6.1 to 52 days). Tumour mass has an influence on specific clearance.

Kinetics in specific patient groups

Age, sex, ethnicity and WHO performance status had no influence on the pharmacokinetics of rituximab.

Paediatric patients

The PK characteristics of MabThera in paediatric patients were similar to those observed in adult patients.

Hepatic/renal impairment

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

Preclinical data

There have been no preclinical studies of the combination of MabThera and methotrexate.

Genotoxicity/carcinogenicity

Genotoxicity and carcinogenicity of MabThera have not been studied.

Reproductive toxicity

Developmental toxicity studies of rituximab performed in cynomolgus monkeys at doses up to 100 mg/kg body weight (from days 20 to 50 of gestation) revealed no evidence of rituximab-induced fetotoxicity. However, pharmacological dose-dependent B cell depletion was observed in the fetal lymphoid tissue. This persisted after birth and was associated with decreased IgG concentrations in the newborns concerned. B cell counts reverted to normal in these animals within six months after birth and did not impair the response to immunisation. Rituximab has been detected in the milk of lactating monkeys.

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

Other information

Incompatibilities

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

MabThera may be mixed only with those medicinal products listed under “Instructions for handling”.

Effects on diagnostic methods

Possible effects on response to vaccines and on diagnostic tests based on the demonstration of antibodies have not been investigated.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the container.

Shelf life after opening

The prepared MabThera solution for infusion in 0.9% sodium chloride solution is physically and chemically stable for 30 days at 2-8°C plus a further 24 hours at ≤30°C. The prepared MabThera solution for infusion in 5% D-glucose solution is physically and chemically stable for 24 hours at 2-8°C plus a further 12 hours at room temperature.

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

Special precautions for storage

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

Keep medicines out of the reach of children.

Instructions for handling

MabThera is a clear, colourless liquid presented in sterile, single-use, preservative- and pyrogen-free rubber-stoppered vials.

Withdraw the required amount of MabThera under aseptic conditions and dilute in an infusion bag containing sterile, non-pyrogenic, 0.9% aqueous saline solution or 5% aqueous dextrose solution to a calculated rituximab concentration of 1 to 4 mg/ml. To mix the solution, gently invert the bag to avoid foaming. As the product contains no antimicrobial preservative or bacteriostatic agent, aseptic technique must be observed. Parenteral medications should be inspected visually for particulate matter or discolouration prior to administration.

Any unused medication remaining after the end of treatment or expiry of the product is to be disposed of in accordance with applicable local regulations.

Authorisation number

54378 (Swissmedic).

Packs

Vial containing 10 ml concentrate for solution for infusion (10 mg/ml): 2 [A]

Vial containing 50 ml concentrate for solution for infusion (10 mg/ml): 1 [A]

Marketing authorisation holder

Roche Pharma (Switzerland) Ltd, Basel.

Date of revision of the text

August 2021.

Revision history

Type of document:	Swiss Information for healthcare professionals ☒				
	Swiss Patient information ☐				
	Export Information for healthcare professionals ☐				
Application ID	Milestone	Version Draft PI (MM/YYYY)	Change	Initials and project number	Sign-off according to SOP-013439 (name, function, date)
102629817	Submission	Draft of March 2020; based on approved version of 21 Jan 2019	Application: Amendment in accordance with the Therapeutic Products Licensing Requirements Ordinance (TPLRO, 2019) (Type II variation/A.109)	Dht/ol/4560	Olivier Leroy DRA Associate, on 9 Mar 2020
102633728, 102633729, 102633730, 102633732, 102633733	Submission	Draft of June 2020; based on approved version of 21 Jan 2019	Application: C.I.6 (paed NHL, paed GPA/ MPA & PV); C.I.101 GPA/MPA maintenance therapy; C.I.4; Art.13	Dht/ol/4690	Dung Ho-Trieu, Senior DRA Manager, on 3 Jun 2020
102633728, 102633729, 102633730, 102633732, 102633733	Response to LoQ	Draft of Jan 2021	Application: C.I.6 (paed NHL, paed GPA/ MPA & PV); C.I.101 GPA/MPA maintenance therapy; C.I.4	Dht/ol/4690	Alene Keller, RA Manager, 19 Feb 2021
102633728, 102633729, 102633730, 102633732, 102633733	Response to positive preliminary decision	Draft of June 2021	Application: C.I.6 (paed NHL, paed GPA/ MPA & PV); C.I.101 GPA/MPA maintenance therapy; C.I.4	Dht/4690	Alene Keller, RA Manager, 24 Jun 2021

102633728, 102633729, 102633730, 102633732, 102633733	Response to text review letter	Draft of August 2021	Application: C.I.6 (paed NHL, paed GPA/ MPA & PV); C.I.101 GPA/MPA maintenance therapy; C.I.4	AK/4690	Alene Keller, RA Manager, 5 Aug 2021
102633728, 102633729, 102633730, 102633732, 102633733	Official decision	17 Aug 2021 (August 2021)	Application: C.I.6 (paed NHL, paed GPA/ MPA & PV); C.I.101 GPA/MPA maintenance therapy; C.I.4	AK/4690	Alene Keller, RA Manager, 10 Sep 2021