PACK INSERT FOR MALAYSIA

MabThera®

Rituximab

1. DESCRIPTION

1.1 Therapeutic / Pharmacologic Class of Drug

Antineoplastic agent

ATC Code: L01XC02

1.2 Type of Dosage Form

Solution for subcutaneous injection

1.3 Route of Administration

Subcutaneous injection

1.4 Sterile / Radioactive Statement

Sterile

1.5 Qualitative and Quantitative Composition

Active ingredient: rituximab

MabThera SC is a colorless to yellowish, clear to opalescent solution supplied in sterile, preservative-free, non-pyrogenic single-dose vials.

MabThera SC contains recombinant human hyaluronidase (rHuPH20), an enzyme used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously (see section 2.5.*Use in Special Populations*, Pregnancy).

Single dose vials contain 1400 mg/11.7 mL (in 15mL vial)

For excipients, see section 4.1 "List of Excipients".

2 CLINICAL PARTICULARS

2.1 Therapeutic Indication(s)

Non-Hodgkin's Lymphoma

MabThera SC is indicated for the treatment of:

- patients with relapsed or chemoresistant low-grade or follicular, CD20-positive, B-cell non-Hodgkin's lymphoma;
- previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy;
- patients with follicular lymphoma as maintenance treatment, after response to induction therapy.
- patients with CD20-positive diffuse large B-cell non-Hodgkin's lymphoma in combination with CHOP *(cyclophosphamide, doxorubicin, vincristine and prednisone)* chemotherapy.

2.2 Dosage and Administration

General

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

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

MabThera should always be administered in an environment where full resuscitation facilities are immediately available and under the close supervision of an experienced healthcare professional.

Premedication consisting of an analgesic/anti-pyretic (e.g., paracetamol /acetaminophen) and an anti-histaminic drug (e.g., diphenhydramine) should always be given before each administration of MabThera.

Premedication with glucocorticoids should also be considered, particularly if MabThera is not given in combination with steroid-containing chemotherapy (see section 2.4 Warnings and Precautions).

Dosage adjustments during treatment:

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

MabThera SC formulation is not intended for intravenous administration (see section 4.2 Special Instructions for Use, Handling and Disposal).

MabThera SC should be injected subcutaneously into the abdominal wall and never into areas where the skin is red, bruised, tender, hard or areas where there are moles or scars. No data are available on performing the injection in other sites of the body, therefore injections should be restricted to the abdominal wall.

During the treatment course with MabThera SC, other medications for subcutaneous administration should preferably be administered at different sites.

MabThera SC 1400 mg injection should be administered over approximately 5 minutes.

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

Standard dosage

Low-grade or Follicular Non-Hodgkin's Lymphoma

Subcutaneous administration:

All patients must always receive their first dose of MabThera by intravenous administration. During their first cycle the patient is at the highest risk of experiencing an infusion/administration related reaction. Beginning therapy with MabThera IV infusion allows management of infusion/administration related reactions by slowing or stopping the intravenous infusion (see section 2.4 Warnings and Precautions). The subcutaneous formulation must only be given at the second or subsequent cycles (see "*First administration: Intravenous formulation" and "Subsequent administrations: Subcutaneous formulation"* sub-sections, below).

First administration: Intravenous formulation:

The first administration of MabThera must always be given by intravenous infusion at a dose of 375 mg/m^2 BSA *(see "Intravenous Formulation Infusion Rate" sub-section, above).*

Subsequent administrations: Subcutaneous formulation:

Patients unable to receive the full MabThera intravenous infusion dose, should continue to receive subsequent cycles with MabThera IV until a full IV dose is successfully administered.

For patients who are able to receive the full MabThera IV infusion dose, the second or subsequent MabThera dose can be given subcutaneously using MabThera SC formulation (see section 2.4 *Warnings and Precautions*).

Initial treatment:

- *Subcutaneous monotherapy*

The recommended dosage of MabThera SC used as monotherapy for adult patients is subcutaneous injection at a fixed dose of 1400 mg irrespective of the patient's BSAonce weekly for for 3 weeks following MabThera IV at week 1 (1st week R-IV then 3 weeks R-SC; 4 weeks in total).

- *Subcutaneous combination therapy*

MabThera SC should be administered on day 0 or day 1 of each chemotherapy cycle after administration of the glucocorticoid component of the chemotherapy, if applicable

The recommended dosage in combination with any chemotherapy is MabThera IV (R-IV) 375 mg/m^2 BSA intravenously for the first cycle followed by subcutaneous injection of MabThera SC at a fixed dose of 1400mg irrespective of the patient's BSA.

- 1st cycle R-IV with CVP + 7 cycles R-SC with CVP (21 days/ cycle)
- 1st cycle R-IV with MCP + 7 cycles R-SC with MCP (28 days/ cycle)
- 1st cycle R-IV with CHOP + 7 cycles R-SC with CHOP (21 days/ cycle); or a total of 6 cycles (1st cycle R-IV then 5 cycles R-SC) if a complete remission is achieved after 4 cycles
- 1st cycle R-IV with CHVP-Interferon + 5 cycles R-SC with CHVP-Interferon (21 days/ cycle)

Re-treatment following relapse:

Patients who have responded to MabThera IV or /SC initially may be treated again with MabThera SC at a fixed dose of 1400mg, administered as a subcutaneous injection once weekly, following a first administration of MabThera given by intravenous infusion at a dose of 375 mg/m2 BSA (1st week R-IV then 3 weeks R-SC; 4 weeks in total) (*see section 3.1.2 Clinical/Efficacy Studies*, Re-treatment, weekly for 4 doses).

Maintenance treatment

Previously untreated patients after response to induction treatment may receive maintenance therapy with MabThera SC given at a fixed dose of 1400mg once every 2 months until disease progression or for a maximum period of two years (12 administrations in total).

Relapsed/refractory patients after response to induction treatment may receive maintenance therapy with MabThera SC given at a fixed dose of 1400mg once every 3 months until disease progression or for a maximum period of two years (8 administrations in total).

Diffuse Large B-cell Non-Hodgkin's Lymphoma:

Subcutaneous administration:

All patients must always receive their first dose of MabThera by intravenous administration. During their first cycle the patient is at the highest risk of experiencing an infusion/administration related reaction. Beginning therapy with MabThera/Rituxan IV infusion allows management of infusion/administration related reactions by slowing or stopping the intravenous infusion (see section 2.4 Warnings and Precautions). The subcutaneous formulation must only be given at the second or subsequent cycles

In patients with diffuse large B cell non-Hodgkin's lymphoma MabThera SC 1400 mg should be used in combination with CHOP (cyclophosphamide, doxorubicin, prednisone and vincristine) chemotherapy. The recommended dosage of MabThera SC is 1400mg, administered on day 1 of each chemotherapy cycle for 8 cycles after IV administration of the glucocorticoid component of CHOP

First administration: Intravenous formulation

The first administration of MabThera must always be given by intravenous infusion at a dose of 375 mg/m2 BSA *(see "Intravenous Formulation Infusion Rate" sub-section, above).*

Subsequent administrations: Subcutaneous formulation

Patients unable to receive the full MabThera intravenous infusion dose, should continue to receive subsequent cycles with MabThera IV until a full IV dose is successfully administered.

For patients who are able to receive the full MabThera IV infusion dose, the second or subsequent MabThera doses can be given subcutaneously using the MabThera SC formulation (see section 2.4 Warnings and Precautions).

The recommended dosage of MabThera SC is a fixed dose of 1400mg, irrespective of the patient's BSA, administered on day 1 of each chemotherapy cycle for 8 cycles (1st cycle R-IV with CHOP + 7 cycles R-SC with CHOP; 8 cycles in total) after IV administration of the glucocorticoid component of CHOP.

2.2.1 Special Dosage Instructions

Children and adolescents:

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

Elderly:

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

2.3 Contraindications

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

2.4 Warnings and Precautions

2.4.1 General

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

Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukaemia Patients

Infusion/administration-related reactions

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

- *Infusion-related reactions for MabThera IV:*

Severe infusion-related reactions (IRRs) with fatal outcome have been reported during post marketing use. Severe IRRs usually manifested within 30 minutes to 2 hours after starting the first MabThera IV infusion, were characterized by pulmonary events and included, in some cases, rapid tumour lysis and features of tumour lysis syndrome in addition to fever, chills, rigors, hypotension, urticaria, angioedema and other symptoms (see section 2.6 Undesirable Effects). Patients with a high tumour burden or with a high number (>25 x 109/L) of circulating malignant cells such as patients with CLL and mantle cell lymphoma may be at higher risk of developing severe IRRs. Infusion reaction symptoms are usually reversible with interruption of the infusion. Treatment of infusion-related symptoms with diphenhydramine and paracetamol/acetaminophen is recommended. Additional treatment with

bronchodilators or IV saline may be indicated. In most cases, the infusion can be resumed at a 50% reduction in rate (e.g. from 100 mg/hour to 50 mg/hour) when symptoms have completely resolved. Most patients who have experienced non-life threatening IRRs have been able to complete the full course of MabThera IV therapy. Further treatment of patients after complete resolution of signs and symptoms has rarely resulted in repeated severe IRRs.

Patients with a high number (>25 x 109/L) of circulating malignant cells or high tumour burden such as patients with CLL and mantle cell lymphoma, who may be at higher risk of especially severe IRRs, should only be treated with extreme caution. These patients should be very closely monitored throughout the first infusion. Consideration should be given to the use of a reduced infusion rate for the first infusion in these patients or a split dosing over two days during the first cycle and any subsequent cycles if the lymphocyte count is still >25 x 109/L.

- *Hypersensitivity reactions / Anaphylaxis*

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

- *Administration-related reactions for MabThera SC*

Local cutaneous reactions, including injection site reactions, have been reported in patients receiving MabThera SC. Symptoms included pain, swelling, induration, haemorrhage, erythema, pruritus and rash (see section 2.6 Undesirable Effects). Some local cutaneous reactions occurred more than 24 hours after the SC drug administration. The majority of local cutaneous reactions seen following administration of the SC formulation were mild or moderate and resolved without any specific treatment.

All patients must always receive their first dose of MabThera by intravenous administration in order to avoid an irreversible administration of the full MabThera SC dose during Cycle 1. During this cycle the patient would have the highest risk of experiencing an IRR that can be treated effectively by slowing or stopping the infusion. The subcutaneous formulation must only be given at the second or subsequent cycles. Patients unable to receive the full MabThera IV infusion dose, should continue to receive subsequent cycles with MabThera IV until a full IV dose is successfully administered. For patients who are able to receive the full MabThera IV infusion dose, the second or subsequent MabThera dose can be given subcutaneously using the MabThera SC formulation (see section 2.2 Dosage and Administration). As with the intravenous formulation, MabThera SC should be administered in an environment where full resuscitation facilities are immediately available and under the close supervision of a health care professional. Premedication consisting of an analgesic/antipyretic and an antihistamine should always be administered before each dose of MabThera SC. Premedication with glucocorticoids should also be considered.

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

Patients should be instructed to contact their treating physician immediately if symptoms that are suggestive of severe hypersensitivity reactions or cytokine release syndrome occur at any time after drug administration.

Pulmonary events

Pulmonary events have included hypoxia, lung infiltration, and acute respiratory failure. Some of these events have been preceded by severe bronchospasm and dyspnea. In some cases, symptoms worsened over time, while in others initial improvement was followed by clinical deterioration. Therefore, patients experiencing pulmonary events or other severe infusion-related symptoms should be closely monitored until complete resolution of their symptoms occurs. Patients with a history of pulmonary insufficiency or those with pulmonary tumour infiltration may be at greater risk of poor outcome and should be treated with increased caution. Acute respiratory failure may be accompanied by events such as pulmonary interstitial infiltration or edema, visible on a chest X-ray. The syndrome usually manifests itself within one or two hours of initiating the first infusion. Patients who experience severe pulmonary events should have their MabThera administration interrupted immediately (see section 2.2 Dosage and Administration) and should receive aggressive symptomatic treatment.

Rapid tumour lysis

MabThera mediates the rapid lysis of benign and malignant CD20-positive cells. Signs and symptoms (e.g. hyperuricemia, hyperkalemia, hypocalcemia, hyperphosphataemia, acute renal failure, elevated LDH) consistent with tumour lysis syndrome (TLS) have been reported to occur after the first MabThera IV infusion in patients with high numbers of circulating malignant lymphocytes. Prophylaxis for TLS should be considered for patients at risk of developing rapid tumour lysis (e.g., patients with a high tumour burden or with a high number [$>25 \times 10^9/L$] of circulating malignant cells such as patients with CLL or mantle cell lymphoma). These patients should be followed closely and appropriate laboratory monitoring performed.

Appropriate medical therapy should be provided for patients who develop signs and symptoms consistent with rapid tumour lysis. Following treatment and complete resolution of signs and symptoms, subsequent MabThera IV therapy has been administered in conjunction with prophylactic therapy for TLS in a limited number of cases.

Cardiovascular

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

Monitoring of blood counts

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

Consideration should be given to the need for regular full blood counts, including platelet counts, during monotherapy with MabThera. When MabThera is given in combination with CHOP or CVP chemotherapy, regular full blood counts should be performed according to usual medical practice.

Infections

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

Hepatitis B infections

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

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

Progressive Multifocal Leukoencephalopathy

Cases of progressive multifocal leukoencephalopathy (PML) have been reported during use of MabThera IV in NHL and CLL (see section 2.6 Undesirable *Effects*, Post Marketing). The majority of patients had received MabThera IV in combination with chemotherapy or as part of a haematopoietic stem cell transplant. Physicians treating patients with NHL or CLL should consider PML in the differential diagnosis of patients reporting neurological symptoms and consultation with a Neurologist should be considered as clinically indicated.

Skin reactions

Severe skin reactions such as toxic epidermal necrolysis and Stevens-Johnson syndrome, some with fatal outcome, have been reported (see section 2.6 Undesirable Effects, *Post Marketing*). In case of such an event with a suspected relationship to MabThera, treatment should be permanently discontinued.

Immunization

The safety of immunization with live viral vaccines, following MabThera IV/SC therapy has not been studied and vaccination with live virus vaccines is not recommended.

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

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

Rheumatoid Arthritis (RA), Granulomatosis with Polyangiitis (Wegener's) (GPA) and Microscopic Polyangiitis (MPA) Patients

The efficacy and safety of MabThera IV for the treatment of autoimmune diseases other than rheumatoid arthritis, granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis have not been established.

Infusion-related reactions

MabThera IV is associated with infusion-related reactions (IRRs), which may be related to release of cytokines and/or other chemical mediators. Premedication consisting of an analgesic/anti-pyretic and an anti-histaminic, should always be administered before each infusion of MabThera. For RA patients, premedication with glucocorticoids should also be administered before each infusion of MabThera IV, in order to reduce the frequency and severity of IRRs (*see section 2.2 Dosage and Administration and section 2.6 Undesirable Effects*).

For RA patients, most infusion-related events reported in clinical trials were mild to moderate in severity. Severe IRRs with fatal outcome have been reported in the post-marketing setting (see section 2.6 *Undesirable Effects, Post- Marketing*). Closely monitor patients with pre-existing cardiac conditions and those who experienced prior cardiopulmonary adverse reactions. The most common symptoms were headache, pruritis, throat irritation, flushing, rash, urticaria, hypertension, and pyrexia. In general, the proportion of patients experiencing any infusion reaction was higher following the first infusion of any treatment course than following the second infusion. Subsequent MabThera IV infusions were better tolerated by patients than the initial infusion. Less than 1% of patients experienced serious IRRs, with most of these reported during the first infusion of the first course (see section 2.6 Undesirable Effects). The reactions reported were usually reversible with a reduction in rate or interruption of MabThera IV infusion, and administration of an anti-pyretic, an antihistamine, and occasionally; oxygen, intravenous saline, bronchodilators, or glucocorticoids as required. Depending on the severity of the IRR and the required interventions, temporarily or permanently discontinue MabThera IV. In most cases, the infusion can be resumed at a 50% reduction in rate (e.g., from 100 mg/hour to 50 mg/hour) when symptoms have completely resolved.

Infusion-related reactions for GPA and MPA patients were similar to those seen for RA patients in clinical trials (see section 2.6 Undesirable *Effects*). For GPA and MPA patients, MabThera IV was given in combination with high doses of glucocorticoids (see section 2.2 Dosage and Administration), which may reduce the incidence and severity of these events (see information for *Rheumatoid Arthritis patients*, above)

Hypersensitivity reactions / Anaphylaxis

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

Cardiovascular

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

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

Infections

Based on the mechanism of action of MabThera and the knowledge that B cells play an important role in maintaining normal immune response, patients may have an increased risk of infection following MabThera IV therapy *(see section 3.1.1, Mechanism of Action)*. MabThera IV should not be administered to patients with an active infection or severely immunocompromised patients (e.g. where levels of CD4 or CD8 are very low). Physicians should exercise caution when considering the use of MabThera IV in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection *(see*

section 2.6 Undesirable Effects). Patients who develop infection following MabThera IV therapy should be promptly evaluated and treated appropriately.

Hepatitis B Infections:

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

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

Skin reactions

Severe skin reactions such as toxic epidermal necrolysis and Stevens-Johnson syndrome, some with fatal outcome, have been reported (see section 2.6 *Undesirable Effects, Post Marketing*). In case of such an event, with a suspected relationship to MabThera IV, treatment should be permanently discontinued.

Progressive multifocal leukoencephalopathy

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

Immunization

The safety of immunization with live viral vaccines following MabThera IV therapy has not been studied. Therefore vaccination with live virus vaccines is not recommended whilst on MabThera IV or whilst peripherally B cell depleted. Patients treated with MabThera IV may receive non-live vaccinations. However, response rates to non-live vaccines maybe reduced.

For RA patients, physicians should review the patient's vaccination status and follow current immunization guidelines prior to MabThera IV therapy. Vaccination should be completed at least 4 weeks prior to first administration of MabThera IV.

In a randomized study, patients with RA treated with MabThera IV and methotrexate had comparable response rates to tetanus recall antigen (39% vs. 42%), reduced rates to pneumococcal polysaccharide vaccine (43% vs. 82% to at least 2 pneumococcal antibody serotypes), and KLH neoantigen (34% vs. 80%), when given at least 6 months after MabThera IV as compared to patients only receiving methotrexate. Should non-live vaccinations be required whilst receiving MabThera IV therapy, these should be completed at least 4 weeks prior to commencing the next course of MabThera IV.

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

Methotrexate naïve RA populations

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

2.4.2 Ability to Drive and Use Machines

No studies on the effect of MabThera on the ability to drive and use machines have been performed although the pharmacological activity and adverse events reported to date do not indicate that such an effect is likely.

2.5 Use in Special Populations

2.5.1 Pregnancy

Intravenous and Subcutaneous Formulations

IgG immunoglobulins are known to cross the placental barrier.

Developmental toxicity studies performed in cynomolgus monkeys revealed no evidence of embryotoxicity in utero. Newborn offspring of maternal animals exposed to MabThera were noted to have depleted B cell populations during the post natal phase. B cell levels in human neonates following maternal exposure to MabThera have not been studied in clinical trials. There are no adequate and well-controlled data from studies in pregnant women, however transient B-cell depletion and lymphocytopenia have been reported in some infants born to mothers exposed to rituximab during pregnancy. For these reasons MabThera should not be administered to pregnant women unless the possible benefit outweighs the potential risk.

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

Subcutaneous Formulation

The subcutaneous formulation contains recombinant human hyaluronidase (rHuPH20) (see section 1.5, Qualitative and Quantitative Composition). Pharmacokinetic and toxicology studies in animals demonstrate reduction in foetal weight and increase in the number of resorptions following injection of rHuPH20, at maternal systemic exposure levels comparable to those that could occur after accidental bolus IV administration of a single vial of the MabThera SC formulation in humans, based on the most conservative assumptions possible (see section 3.3 *Preclinical Safety,Subcutaneous Formulation*).

To reduce the additional potential risk of embryofoetal toxicity resulting from exposure to rHuPH20, patients who conceive whilst treated with MabThera SC should discontinue treatment with the SC formulation.

2.5.2 Nursing Mothers

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

2.5.3 Pediatric Use

The safety and effectiveness of MabThera in pediatric patients have not been established. Hypogammaglobulinaemia has been observed in pediatric patients treated with MabThera, in some cases severe and requiring long-term immunoglobulin substitution therapy. The consequences of long term B cell depletion in pediatric patients are unknown.

2.6 Undesirable Effects

2.6.1 Clinical Trials

Experience from Clinical Trials in Hemato-Oncology

Intravenous Formulation

The frequencies of adverse drug reactions (ADRs) reported with MabThera IV alone or in combination with chemotherapy are summarised in the tables below and are based on data from clinical trials. These ADRs had either occurred in single arm studies or had occurred with at least a 2% difference compared to the control arm in at least one of the major randomized clinical trials. ADRs are added to the appropriate category in the tables below according to the highest incidence seen in any of the major clinical trials. Within each frequency grouping ADRs are listed in descending order of severity. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), and uncommon (≥ 1/1,000 to < 1/100).

***MabThera* IV Monotherapy/Maintenance Therapy**

The ADRs in Table 1 are based on data from single-arm studies including 356 patients with low-grade or follicular lymphoma, treated with MabThera IV weekly as single agent for the treatment or re-treatment of non-Hodgkin's lymphoma (see section 3.1.2 Clinical/Efficacy Studies). The table also contains ADRs based on data from 671 patients with follicular lymphoma who received MabThera IV as maintenance therapy for up to 2 years following response to initial induction with CHOP, R-CHOP, R-CVP or R-FCM (see section 3.1.2 Clinical/Efficacy Studies). The ADRs were reported up to 12 months after treatment with monotherapy and up to 1 month after treatment with MabThera IV maintenance.

Table 1 Summary of ADRs Reported in Patients with Low-Grade or Follicular Lymphoma Receiving MabThera/Rituxan IV Monotherapy (n = 356) [42] or MabThera/Rituxan IV Maintenance Treatment (n = 671) [91, 142] in Clinical Trials.

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

		dysphagia , stomatitis, constipation, dyspepsia, anorexia, throat irritation	
Skin and subcutaneous tissue disorders	pruritus, rash	urticaria , +alopecia, sweating, night sweats	
Musculoskeletal, connective tissue and bone disorders		hypertonia, myalgia , arthralgia , back pain , neck pain, pain	
General disorders and administration site conditions	fever , chills , asthenia , headache	tumour pain, flushing, malaise, cold syndrome	infusion site pain
Investigations	decreased IgG levels		

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

MabThera IV in Combination with Chemotherapy in NHL and CLL

The ADRs listed in Table 2 are based on MabThera IV-arm data from controlled clinical trials that occurred in addition to those seen with monotherapy / maintenance therapy and/or at a higher frequency grouping: 202 patients with diffuse large B-cell lymphoma (DLBCL) treated with R-CHOP, and from 234 and 162 patients with follicular lymphoma treated with R-CHOP or R-CVP, respectively and from 397 previously untreated CLL patients and 274 relapsed/refractory CLL patients, treated with MabThera IV in combination with fludarabine and cyclophosphamide (R-FC) (*see section 3.1.2 Clinical/Efficacy Studies*).

Table 2 Summary of Severe ADRs Reported in Patients Receiving R-CHOP in DLBCL (n=202), R-CHOP in Follicular Lymphoma (n=234), R-CVP in Follicular Lymphoma (n=162), R-FC in Previously Untreated (n=397) or Relapsed/Refractory (n=274) Chronic Lymphocytic Leukaemia

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

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

Frequency count was based on only severe reactions defined in clinical trials as ≥ grade 3 NCI common toxicity criteria

Only the highest frequency observed in any trial is reported

prolonged and/or delayed onset neutropenia after completion of an R-FC course in previously untreated or relapsed/refractory CLL

The following terms have been reported as adverse events, however, were reported at a similar (<2% difference between the groups) or lower incidence in the MabThera IV-arms compared to control arms: Haematotoxicity, neutropenic infection, urinary tract infection, septic shock, superinfection lung, implant infection, septicaemia staphylococcal, lung infection, rhinorrheoa, pulmonary oedema, cardiac failure, sensory disturbance, venous thrombosis, mucosal inflammation nos, influenza-like illness, oedema lower limb, abnormal ejection fraction, pyrexia, general physical health deterioration, fall, multi-organ failure, venous thrombosis deep limb, positive blood culture, diabetes mellitus inadequate control.

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

Subcutaneous Formulation

Local cutaneous reactions, including injection site reactions, were very common (≥ 1/10) in patients receiving MabThera SC. In the phase 3 SABRINA (BO22334) study, local cutaneous reactions were reported in up to 23% of patients receiving MabThera SC. The most common local cutaneous reactions in the MabThera SC arm were injection site erythema (13%), injection site pain (*8*%), and injection site oedema (4%). Similar events were observed in the SAWYER (BO25341) study and were reported in up to 42% of patients in the MabThera SC arm. The most common local cutaneous reactions were injection site erythema (26%), injection site pain (16%), and injection site swelling (5%). Events seen following subcutaneous administration were mild or moderate, apart from one patient in the SABRINA study who reported a local cutaneous reaction of Grade 3 intensity (injection site rash) and two patients in the SAWYER study who experienced Grade 3 local cutaneous reactions (injection site erythema, injection site pain, and injection site swelling). Local cutaneous reactions of any Grade in the MabThera SC arm were most common during the first subcutaneous cycle (Cycle 2), followed by the second, and the incidence decreased with subsequent injections.

The safety profile of MabThera SC was otherwise comparable to that of the IV formulation.

No cases of anaphylaxis or severe hypersensitivity reactions, cytokine release syndrome or tumour lysis syndrome were observed following subcutaneous administration during the MabThera/Rituxan SC development program.

Further information on selected, serious adverse drug reactions

Intravenous Formulation

Administration-related reactions

Monotherapy - 4 weeks treatment

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

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

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

Subcutaneous Formulation

The risk of acute administration-related reactions associated with the subcutaneous formulation of MabThera was assessed in three clinical studies.

In the SparkThera (BP22333) study no severe administration-related reactions were reported.

In the SABRINA (BO22334) study severe administration-related reactions (Grade≥=3) were reported in two patients (1%) following MabThera SC administration. These events were Grade 3 injection site rash and dry mouth.

In the SAWYER (BO25341), study severe administration-related reactions (Grade≥=3) were reported in four patients (5%) following MabThera/Rituxan SC administration. These events were Grade 4 thrombocytopenia and Grade 3 anxiety, injection-site erythema and urticaria.

Infections

Monotherapy 4 weeks treatment

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

Maintenance Treatment (NHL) up to 2 years

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

Data from clinical trials included cases of fatal PML in NHL patients that occurred after disease progression and retreatment (see section 2.4 Warnings and Precautions).

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

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

In the R-CHOP study the overall incidence of Grade 2 to 4 infections was 45.5% in the R-CHOP group and 42.3% in the CHOP group. Grade 2 to 4 fungal infections were more frequent in the R-CHOP group (4.5% *vs.* 2.6% in the CHOP group); this difference was due to a higher incidence of localized Candida infections during the treatment period. The incidence of Grade 2 to 4 herpes zoster was higher in the R-CHOP group (4.5%) than in the CHOP group (1.5%). The proportion of patients with Grade 2 to 4 infections and/or febrile neutropenia was 55.4% in the R-CHOP group and 51.5% in the CHOP group.

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

Hematologic events

Monotherapy 4 weeks treatment

Severe (Grade 3 and 4) neutropenia was reported in 4.2% of patients, severe anemia was reported in 1.1% of patients and severe thrombocytopenia was reported in 1.7% of patients.

Maintenance Treatment (NHL) up to 2 years

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

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

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

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

Cardiovascular events

Monotherapy 4 weeks treatment

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

Maintenance Treatment (NHL) up to 2 years

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

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

In the R-CHOP study the incidence of Grade 3 and 4 cardiac arrhythmias, predominantly supraventricular arrhythmias such as tachycardia and atrial flutter/fibrillation, was higher in the R-CHOP group (6.9%) as compared to the CHOP group (1.5%). All of these arrhythmias either occurred in the context of a MabThera IV infusion or were associated with predisposing conditions such as fever, infection, acute myocardial infarction or pre-existing respiratory and cardiovascular disease (see section 2.4 Warnings and Precautions). No difference between the R-CHOP and CHOP group was observed in the incidence of other Grade 3 and 4 cardiac events including heart failure, myocardial disease and manifestations of coronary artery disease.

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

IgG levels

Maintenance Treatment (NHL) up to 2 years

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

Neurologic events

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

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

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

Subpopulations

Monotherapy- 4 weeks treatment

Elderly patients (≥65 years)

The incidence of any ADR and of Grade 3 and 4 ADRs was similar in elderly (≥ 65 years of age) and younger patients (88.3% vs. 92.0% for any ADR and 16.0% vs. 18.1% for Grade 3 and 4 ADRs).

Combination Therapy

Elderly patients (≥ 65 years):

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

Bulky disease

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

Re-treatment with monotherapy

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

Experience from Rheumatoid Arthritis Clinical Trials

Intravenous Formulation

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

The ADRs listed in Table 3 are based on data from placebo-controlled periods of four multicenter, RA clinical trials. The patient populations receiving MabThera IV differed between studies, ranging from early active RA patients who were methotrexate (MTX) naïve, through MTX inadequate responders (MTX-IR) to patients who had inadequate response to anti- tumour necrosis factor (TNF) therapies (TNF-IR) *(see section 3.1.2 Clinical/Efficacy Studies).*

Patients received 2 x 1000mg or 2 x 500 mg of MabThera IV separated by an interval of two weeks, in addition to methotrexate (10 to 25 mg/week) *(see section 2.2 Dosage and Administration, Rheumatoid Arthritis).*

The ADRs listed in Table 3 are those which occurred at a rate of at least 2 %, with at least a 2% difference compared to the control arm and are presented regardless of dose. Frequencies in Table 3 and the corresponding footnote are defined as very common (≥1/10), common (≥1/100 to <1/10) and uncommon ((≥1/1000 to <1/100).

Table 3 Summary of ADRs Reported in Patients with Rheumatoid Arthritis within Control Period of Clinical Trials †

System Organ Class	Very Common	Common
Infections and Infestations	Upper respiratory tract infection, Urinary tract infection	Bronchitis, Sinusitis, Gastroenteritis, Tinea pedis
Immune System Disorders/ General disorders and administration site conditions	Infusion related reactions	*****Infusion related reactions: (Hypertension, Nausea, Rash, Pyrexia, Pruritus, Urticaria, Throat irritation, Hot flush, Hypotension, Rhinitis, Rigors, Tachycardia, Fatigue, Oropharyngeal pain, Peripheral Oedema, Erythema)
Metabolism and Nutritional Disorders		Hypercholesterolemia
Nervous System disorders	Headache	Paraesthesia, Migraine, Dizziness, Sciatica
Skin & Subcutaneous Tissue disorders		Alopecia
Psychiatric Disorders		Depression, Anxiety
Gastrointestinal Disorders		Dyspepsia, Diarrhoea, Gastro esophageal reflux, Mouth ulceration, Abdominal pain upper
Musculoskeletal and connective tissue disorders		Arthralgia/Musculoskeletal pain, Osteoarthritis, Bursitis

† This table includes all events with an incidence difference of ≥ 2 % for MabThera IV compared to placebo

* In addition, medically significant events reported uncommonly associated with IRRs include: generalized oedema, bronchospasm, wheezing, laryngeal oedema, angioneurotic oedema, generalized pruritus, anaphylaxis, anaphylactoid reaction.

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

Multiple courses:

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

Further information on selected adverse drug reactions:

Infusion-related reactions:

The most frequent ADRs following receipt of MabThera IV in RA clinical studies were IRRs. Among the 3095 patients treated with MabThera IV, 1077 (35%) experienced at least one IRR. The vast majority of IRRs were CTC Grade 1 or 2. In clinical studies less than 1% (14/3095 patients) of patients with RA who received an infusion of MabThera IV at any dose experienced a serious IRR. There were no CTC Grade 4 IRRs and no deaths due to IRRs in the clinical studies (*see section 2.6Undesirable Effects, Post-Marketing*). The proportion of CTC Grade 3 events, and IRRs leading to withdrawal decreased by course and were rare from course 3 onwards.

Signs and/or symptoms suggesting an IRR (*i.e., nausea, pruritus, fever, urticaria/rash, chills, pyrexia, rigors, sneezing, angioneurotic oedema, throat irritation, cough and bronchospasm, with or without associated hypotension or hypertension*) were observed in 720/3095 (23%) patients following the first infusion of the first exposure to MabThera IV. Premedication with IV glucocorticoid significantly reduced the incidence and severity of these events (*see section 2.4 Warnings and Precautions*).

Infections:

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

Malignancies:

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

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

Intravenous Formulation

In the GPA and MPA clinical study, 99 patients were treated with MabThera IV (375 mg/m^2, once weekly for 4 weeks) and glucocorticoids (*see section 3.1.2 Clinical/Efficacy Studies*).

The ADRs listed in Table 4 were all adverse events which occurred at an incidence of ≥ 10% in the MabThera IV-treated group. Frequencies in Table 4 are defined as very common (≥1/10*).*

Table 4 Incidence of Very Common (≥ 10%) ADRs for MabThera-IV treated GPA and MPA Patients in Clinical Study up to Month 6*

Adverse reactions	Rituximab n = 99	Cyclophosphamide n = 98
Infections and infestations		
Infections[a]	61 (61.6%)	46 (46.9%)
Gastrointestinal disorders		
Nausea	18 (18.2%)	20 (20.4%)
Diarrhea	17 (17.2%)	12 (12.2%)
Nervous system disorders		
Headache	17 (17.2%)	19 (19.4%)
Musculoskeletal and connective tissue disorders		
Muscle spasm	17 (17.2%)	15 (15.3%)
Arthralgia	13 (13.1%)	9 (9.2%)
Blood and lymphatic system disorders		
Anemia	16 (16.2%)	20 (20.4%)
Leukopenia	10 (10.1%)	26 (26.5%)
General disorders and administration site conditions	16 (16.2%)	6 (6.1%)

Peripheral edema Fatigue	13 (13.1%)	21 (21.4%)
Psychiatric disorders Insomnia	14 (14.1%)	12 (12.2%)
Investigations Increased ALT	13 (13.1%)	15 (15.3%)
Respiratory, thoracic and mediastinal disorders Cough, Epistaxis, Dyspnea	13 (13.1%) 11 (11.1%) 10 (10.1%)	11 (11.2%) 6 (6.1%) 11 (11.2%)
Vascular disorders Hypertension	12 (12.1%)	5 (5.1%)
Immune system disorders Infusion related reactions[b]	12 (12.1%)	11 (11.2%)
Skin and subcutaneous tissue disorders Rash	10 (10.1%)	17 (17.3%)

*The study design allowed for crossover or treatment by best medical judgment, and 13 patients in each treatment group received a second therapy during the 6 month study period.

[a]Most common infections in the rituximab group included upper respiratory tract infections, urinary tract infections, and herpes zoster.

[b]Most common terms reported in the rituximab group included cytokine release syndrome, flushing, throat irritation, and tremor.

Further information on selected adverse drug reactions:

Infusion-related reactions:

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

Infections:

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

Malignancies:

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

2.6.1 *Laboratory Abnormalities*

Intravenous Formulation

Rheumatoid Arthritis Patients

Hypogammaglobulinaemia (IgG or IgM below the lower limit of normal) has been observed in RA patients treated with MabThera IV. There was no increased rate in overall infections or serious infections after the development of low IgG or IgM. Events of neutropenia associated with MabThera IV treatment, the majority of which were transient and mild or moderate in severity, were observed in clinical trials in RA patients after the first course of treatment. Neutropenia can occur several months after the administration of MabThera IV.

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

Granulomatosis with Polyangiitis (Wegener's) (GPA) and Microscopic Polyangiitis (MPA) Patients

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

At 6 months, in the MabThera/Rituxan IV group, 27%, 58% and 51% of patients with normal immunoglobulin levels at baseline, had low IgA, IgG and IgM levels, respectively compared to 25%, 50% and 46%, respectively in the cyclophosphamide group. There was no increased rate in overall infections or serious infections in patients with low IgA, IgG or IgM.

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

2.6.2 Post Marketing

Intravenous Formulation

Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukaemia Patients

The reporting frequencies in this section (rare, very rare) are based on estimated marketed exposures and largely data largely derived from spontaneous reports.

Additional cases of severe IRRs have been reported during post-marketing use of MabThera IV (see section 2.4 Warnings and Precautions).

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

Cardiovascular system:

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

Respiratory system:

Respiratory failure/insufficiency and lung infiltration in the context of IRRs have been observed *(see section 2.4 Warnings and Precautions)*. In addition to pulmonary events associated with infusions, interstitial lung disease, some with fatal outcome, have been reported.

Blood and lymphatic system:

Cases of infusion-related acute reversible thrombocytopenia have been reported.

Skin and appendages:

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

Nervous system:

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

Cases of cranial neuropathy with or without peripheral neuropathy have been reported rarely. Signs and symptoms of cranial neuropathy, such as severe vision loss, hearing loss, loss of other senses and facial nerve palsy, occurred at various times up to several months after completion of MabThera IV therapy.

Body as a whole:

Serum sickness-like reactions have been reported rarely.

Infections and infestations:

Cases of hepatitis B reactivation have been reported, the majority of which were in subjects receiving MabThera/Rituxan IV in combination with cytotoxic chemotherapy (see section 2.4 Warnings and Precautions).

Other serious viral infections, either new, reactivation or exacerbation, some of which were fatal, have been reported with MabThera/Rituxan IV treatment. The majority of patients had received MabThera/Rituxan IV in combination with chemotherapy or as part of a hematopoietic stem cell transplant. Examples of these serious viral infections are infections caused by the herpes viruses (cytomegalovirus [*CMV*], *varicella zoster virus and h*erpes simplex virus), JC virus (progressive multifocal leukoencephalopathy [*PML*] see section 2.4 Warnings and Precautions) and hepatitis C virus.

Progression of Kaposi's sarcoma has been observed in MabThera/Rituxan IV-exposed patients with pre-existing Kaposi's sarcoma. These cases occurred in non-approved indications and the majority of patients were HIV positive.

Gastro-intestinal system:

Gastro-intestinal perforation, in some cases leading to death, has been observed in patients receiving MabThera IV in combination with chemotherapy for non-Hodgkin's lymphoma.

Rheumatoid Arthritis (RA), Granulomatosis with Polyangiitis (Wegener's) (GPA) and Microscopic Polyangiitis (MPA) Patients

As part of the continuing post-marketing surveillance of MabThera IV safety, the following have been observed in the RA setting and are also expected, if not already observed, in GPA/MPA patients:

Infections and Infestations:

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

Body as a whole:

Serum sickness-like reaction has been reported.

Skin and subcutaneous tissue disorders:

*e*pidermal *n*ecrolysis and Stevens–Johnson syndrome some with fatal outcome have been reported very rarely.

Blood and lymphatic system disorders:

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

Nervous system:

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

General disorders and administration site conditions:

Severe IRRs some with fatal outcome have been reported (see section 2.6 *Undesirable Effects*, Clinical Trials).

2.6.2.1 Laboratory Abnormalities

Intravenous Formulation

Non-Hodgkin's Lymphoma

Blood and lymphatic system:

Rarely the onset of neutropenia has occurred more than four weeks after the last infusion of MabThera.

Post Marketing:

In studies of MabThera/Rituxan IV in patients with Waldenstrom's macroglobulinemia, 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.

2.7 Overdose

Intravenous and Subcutaneous Formulations

Limited experience with doses higher than the approved intravenous doses of MabThera IV is available from clinical trials in humans. The highest IV dose tested in humans to date is 5000mg (2250 mg/m2), tested in a dose escalation study in patients with chronic lymphocytic leukaemia. No additional safety signals were identified. Patients who experience overdose should have immediate interruption of their infusion and be closely monitored.

Three patients in the MabThera SC SABRINA (BO22334) study were inadvertently administered the SC formulation through IV route up to a maximum rituximab dose of 2780 mg with no untoward effect. Patients who experience overdose or medication error with MabThera SC should be closely monitored.

Consideration should be given to the need for regular monitoring of blood cell count and for increased risk of infections while patients are B cell-depleted

2.8 Interactions with other Medicinal Products and other Forms of Interaction

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

In CLL patients, co-administration with MabThera IV did not appear to have an effect on the pharmacokinetics of fludarabine or cyclophosphamide, in addition; there was no apparent effect of fludarabine and cyclophosphamide on the pharmacokinetics of MabThera.
Co-administration with methotrexate had no effect on the pharmacokinetics of MabThera IV in RA patients.
Patients with human anti-mouse antibody (HAMA) or human anti-chimeric antibody (HACA) titers may develop allergic or hypersensitivity reactions when treated with other diagnostic or therapeutic monoclonal antibodies.
In the RA clinical trial program, 373 MabThera IV-treated patients received subsequent therapy with other disease-modifying antirheumatic drugs (DMARDs), of whom 240 received a biologic DMARD. In these patients the rate of serious infection while on MabThera IV (prior to receiving a biologic DMARD) was 6.1 per 100 –patients- years compared to 4.9 per 100 patients years following subsequent treatment with the biologic DMARD.

3 PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 Pharmacodynamic Properties

3.1.1 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 hemopoietic stem cells, pro-B-cells, normal plasma cells or other normal tissue. The antigen is expressed on >95% of all B-cell non-Hodgkin's lymphomas (NHLs). Following antibody binding, CD20 is not internalized or shed from the cell membrane into the environment. CD20 does not circulate in the plasma as a free antigen and, thus, does not compete for antibody binding.
Rituximab binds to the CD20 antigen on B-lymphocytes and initiates immunologic reactions that mediate B-cell lysis. Possible mechanisms of cell lysis include complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), and induction of apoptosis. Finally, in vitro studies have demonstrated that rituximab sensitizes drug-resistant human B-cell lymphoma lines to the cytotoxic effects of some chemotherapeutic agents.
Peripheral B-cell counts declined to levels below normal following the first dose of MabThera. In patients treated for hematological malignancies, B cell recovery began within 6 months of treatment and generally returning to normal levels within 12 months after completion of therapy, although in some patients this may take longer (*see section 2.6 Undesirable Effects, Clinical Trials, Experience from Clinical Trials in Haemato-Oncology*).
In patients with rheumatoid arthritis, the duration of peripheral B-cell depletion was variable. The majority of patients received further treatment prior to full B-cell repletion. A small proportion of patients had prolonged peripheral B-cell depletion lasting 2 years or more after their last dose of MabThera IV.
In GPA and MPA patients, peripheral blood CD19 B-cells depleted to less than 10 cells/µl following the first two infusions of rituximab and remained at that level in most patients through month 6.
Of 67 patients evaluated for human anti-mouse antibody (HAMA), none were positive. Of 356 non-Hodgkin's lymphoma patients evaluated for human anti-chimeric antibody (HACA) 1.1% (4 patients) were positive.

3.1.2 Clinical / Efficacy Studies

Intravenous Formulation

Low-grade FollicularNon-Hodgkin's Lymphoma

MabThera/Rituxan IV Monotherapy

Initial treatment, weekly for 4 doses

In the pivotal study, 166 patients with relapsed or chemoresistant low-grade or follicular B-cell NHL received 375 mg/m^2 of MabThera as an IV infusion weekly for four doses. The overall response rate (ORR) in the intent-to-treat (ITT) population was 48% ($CI_{95\%}$ 41% – 56%) with a 6% complete response (CR) and a 42% partial response (PR) rate. The projected median time to progression (TTP) for responding patients was 13.0 months.
In a subgroup analysis, the ORR was higher in patients with IWF B, C, and D histologic subtypes as compared to IWF A subtype (58% *vs.* 12%), higher in patients whose largest lesion was <5 cm versus >7 cm in greatest diameter (53% *vs.* 38%), and higher in patients with chemosensitive relapse as compared to chemoresistant (defined as duration of response <3 months) relapse (50% *vs.* 22%). ORR in patients previously treated with autologous bone marrow transplant (ABMT) was 78% *vs.* 43% in patients with no ABMT. Neither age, sex, lymphoma grade, initial diagnosis, presence or absence of bulky disease, normal or high LDH nor presence of extranodal disease had a statistically significant effect (Fisher's exact test) on response to MabThera IV.
A statistically significant correlation was noted between response rates and bone marrow involvement. Forty percent of patients with bone marrow involvement responded compared to 59% of patients with no bone marrow involvement (p=0.0186). This finding was not supported by a stepwise logistic regression analysis in which the following factors were identified as prognostic factors: histologic type, bcl-2 positivity at baseline, resistance to last chemotherapy and bulky disease.
Initial treatment, weekly for 8 doses
In a multi-center, single-arm study, 37 patients with relapsed or chemoresistant, low grade or follicular B-cell NHL received 375 mg/m^2 of MabThera as IV infusion weekly for eight doses. The ORR was 57% ($CI_{95\%}$ 41% – 73%; CR 14%, PR 43%) with a projected median TTP for responding patients of 19.4 months (range 5.3 to 38.9 months).
Initial treatment, bulky disease, weekly for 4 doses
In pooled data from three studies, 39 patients with relapsed or chemoresistant, bulky disease (single lesion ≥10 cm in diameter), low grade or follicular B-cell NHL received 375 mg/m^2 of MabThera as IV infusion weekly for four doses. The ORR was 36% ($CI_{95\%}$ 21% – 51%; CR 3%, PR 33%) with a median TTP for responding patients of 9.6 months (range 4.5 to 26.8 months).
Re-treatment, weekly for 4 doses
In a multi-center, single-arm study, 58 patients with relapsed or chemoresistant low grade or follicular B-cell NHL, who had achieved an objective clinical response to a prior course of MabThera IV, were re-treated with 375 mg/m^2 of MabThera as i.v. infusion weekly for four doses. Three of the patients had received two courses of MabThera IV before enrollment and thus were given a third course in the study. Two patients were re-treated twice in the study. For the 60 re-treatments on study, the ORR was 38% ($CI_{95\%}$ 26% – 51%; 10% CR, 28% PR) with a projected median TTP for responding patients of 17.8 months (range 5.4 – 26.6). This compares favorably with the TTP achieved after the prior course of MabThera IV (12.4 months).

MabThera/Rituxan IV in Combination With Chemotherapy

Initial treatment
In an open-label randomized trial, a total of 322 previously untreated patients with follicular lymphoma were randomized to receive either CVP chemotherapy (cyclophosphamide 750 mg/m^2, vincristine 1.4 mg/m^2 up to a maximum of 2 mg on day 1, and prednisolone 40 mg/m^2/day on days 1-5) every 3 weeks for 8 cycles or MabThera IV 375 mg/m^2 in combination with CVP (R-CVP). MabThera IV was administered on the first day of each treatment cycle. A total of 321 patients (162 R-CVP, 159 CVP) received therapy and were analyzed for efficacy.
The median follow-up of patients was 53 months. R-CVP led to a significant benefit over CVP for the primary endpoint, time to treatment failure (27 months vs. 6.6 months, p < 0.0001, log-rank test). The proportion of patients with a tumour response (CR, CRu, PR) was significantly higher (p< 0.0001 Chi-Square test) in the R-CVP group (80.9%) than the CVP group (57.2%). Treatment with R-CVP significantly prolonged the time to disease progression or death compared to CVP, 33.6 months and 14.7 months, respectively (p < 0.0001, log-rank test). The median duration of response was 37.7 months in the R-CVP group and was 13.5 months in the CVP group (p < 0.0001, log-rank test). The difference between the treatment groups with respect to overall survival showed a strong clinical benefit (p=0.029, log-rank test stratified by center): survival rates at 53 months were 80.9% for patients in the R-CVP group compared to 71.1% for patients in the CVP group.
Results from three other randomized trials using MabThera IV in combination with chemotherapy regimen other than CVP (CHOP, MCP, CHVP/Interferon-α) also demonstrated significant improvements in response rates, time-dependent parameters as well as in overall survival. Key results from all four studies are summarized in Table 5 below.

Table 5 Summary of *K*ey *R*esults from *F*our *P*hase III *R*andomized *S*tudies *E*valuating the *B*enefit of MabThera/Rituxan *IV* with *D*ifferent *C*hemotherapy *R*egimens in *F*ollicular *L*mphoma

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

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

MabThera/Rituxan IV Maintenance Therapy

Previously untreated follicular NHL
In a prospective, open label, international, multi-center, phase III trial 1193 patients with previously untreated advanced follicular lymphoma received induction therapy with R-CHOP (n=881), R-CVP (n=268) or R-FCM (n=44), according to the investigators' choice. A total of 1078 patients responded to induction therapy, of which 1018 were randomized to MabThera IV maintenance therapy (n=505) or observation (n=513). The two treatment groups were well balanced with regards to baseline characteristics and disease status. MabThera IV maintenance treatment consisted of a single infusion of MabThera IV at 375 mg/m^2 BSA given every 2 months until disease progression or for a maximum period of two years.
After a median observation time of 25 months from randomization, maintenance therapy with MabThera IV resulted in a clinically relevant and statistically significant improvement in the primary endpoint of investigator assessed progression-free survival (PFS) as compared to no maintenance therapy in patients with previously untreated follicular NHL. This improvement in PFS was confirmed by an independent review committee (IRC) (see Table 6 below).
Significant benefit from maintenance treatment with MabThera IV was also seen for the secondary endpoints event-free survival (EFS), time to next anti-lymphoma treatment (TNLT) time to next chemotherapy (TNCT) and overall response rate (ORR) ((see Table 6 below 6).
The updated analysis corresponding to a median observation time of 73 months from randomization confirm the results of the primary analysis (see Table 6 below).

Table 6 – Overview of Efficacy Results for Maintenance MabThera IV vs. Observation (25 and 73 Months Median Observation-Time)

Efficacy Parameter	Primary Analysis[a]		Updated Analysis[b]	
	Observation N = 513	Rituximab Maintenance N = 505	Observation N = 513	Rituximab Maintenance N = 505
Primary Endpoint Progression-free Survival[c]				
Median time to event (months)	NR	NR	49	NR
p value (stratified log-rank test)	p < 0.0001		p < 0.0001	
HR [95% CI] (stratified)	0.50 [0.39;0.64]		0.58 [0.48;0.69]	

Secondary Endpoints				
Overall Survival				
Median time to event (months)	NR	NR	NR	NR
p value (stratified log-rank test)	p = 0.7246		p = 0.8959	
HR [95% CI] (stratified)	0.89 [0.45;1.74]		1.02 [0.71;1.47]	
Overall Response Rate at End of Maintenance/Observation				
Patients assessed at end of treatment	398	389	509	500
Responders (CR/Cru, PR)	219/398 (55%)	288/389 (74%)	309/509 (61%)	395/500 (79%)
p value (χ^2 test)	p < 0.0001		p < 0.0001	
Non-responders	179/398 (45%)	101/389 (26%)	200/509 (40%)	105/500 (21%)
Patients with complete response (CR/CRu)	190 (48%)	260 (67%)	268 (53%)	361 (72%)
partial response (PR)	29 (7%)	28 (7%)	41 (8%)	34 (7%)
stable disease (SD)	1 (<1%)	0 (0%)	1 (<1%)	1 (<1%)
progressive disease (PD)	162 (41%)	79 (20%)	181 (36%)	86 (17%)
Event-free Survival				
Median time to event (months)	38	NR	48	NR
p value (stratified log-rank test)	p < 0.0001		p < 0.0001	
HR [95% CI] (stratified)	0.54 [0.43;0.69]		0.61 [0.51;0.72]	
Time to Next Anti-Lymphoma Treatment				
Median time to event (months)	NR	NR	71	NR
p value (stratified log-rank test)	p = 0.0003		p < 0.0001	
HR [95% CI] (stratified)	0.61 [0.46;0.80]		0.63 [0.52;0.76]	
Time to Next Chemotherapy Treatment				
Median time to event (months)	NR	NR	85	NR
p value (stratified log-rank test)	p = 0.0011		p = 0.0006	
HR [95% CI] (stratified)	0.60 [0.44;0.82]		0.70 [0.57;0.86]	
Transformation Rate at First Progression				
Patients with progression	173	91	278	186
Patients with transformation	19/513 (4%)	11/505 (2%)	24/513 (5%)	16/505 (3%)

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

MabThera IV maintenance treatment provided consistent benefit in all subgroups tested: gender (male, female), age (<60 years, ≥60 years), FLIPI score (1, 2 or 3), induction therapy (R-CHOP, R-CVP or R-FCM) and regardless of the quality of response to induction treatment (CR or PR).

Relapsed/Refractory follicular NHL

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

The final efficacy analysis included all patients randomized to both parts of the study. After a median observation time of 31 months for patients randomised to the induction phase, R-CHOP significantly improved the outcome of patients with relapsed/refractory follicular NHL when compared to CHOP (see Table 7 below).

Table 7 – Induction Phase: Overview of Efficacy Results for CHOP vs. R-CHOP (31 Months Median Observation Time)

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

[1)] Estimates were calculated by hazard ratios
[2)] Last tumour response as assessed by the investigator. The "primary" statistical test for "response" was the trend test of CR versus PR versus non-response (p < 0.0001)
Abbreviations: NA, not available; NR, not reached; mo, months; ORR: overall response rate; CR: complete response; PR: partial response; OS: overall survival: PFS: progression free survival

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

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

Table 8 - Maintenance Phase: Overview of Efficacy Results MabThera IV vs. Observation (28 Months Median Observation Time)

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

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

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

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

Diffuse Large B-cell Non-Hodgkin's Lymphoma

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

The final efficacy analysis included all randomized patients (197 CHOP, 202 R-CHOP), and had a median follow-up duration of approximately 31 months. The two

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

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

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

Subcutaneous formulation

Previously Untreated Follicular Non-Hodgkin's Lymphoma BO22334 (SABRINA)

A two-stage phase III, international, multi-center, randomized, controlled, open-label study was conducted in patients with previously untreated follicular lymphoma, to investigate the non-inferiority of the pharmacokinetic profile, together with efficacy and safety of MabThera SC in combination with CHOP or CVP vs. MabThera IV in combination with CHOP or CVP followed by MabThera /Rituxan maintenance therapy. The objective of the first stage was to establish the MabThera/Rituxan SC dose that resulted in comparable rituximab serum C_{trough} levels compared with MabThera IV, when given as part of induction treatment every 3 weeks for 8 cycles *(see section 3.2* Pharmacokinetic Properties, Distribution). Stage 1 enrolled previously untreated patients with CD20-positive, follicular lymphoma (FL) Grade 1, 2 or 3a (n=127). Patients with a response at the end of induction therapy received maintenance therapy with the corresponding formulation (intravenous or subcutaneous) used in the induction treatment, every 8 weeks for 24 months.

The objective of Stage 2 was to provide additional efficacy and safety data for MabThera/Rituxan SC compared with MabThera/Rituxan IV using the 1400 mg subcutaneous dose established in Stage 1. Previously untreated patients with CD20-positive, follicular lymphoma Grade 1, 2 or 3a (n=283) were enrolled in Stage 2.

The overall study design was identical across Stage 1 and Stage 2. Patients were randomized into the following two treatment groups:

- MabThera SC arm (n=205): 1st cycle MabThera IV plus 7 cycles of MabThera SC in combination with up to 8 cycles of CHOP or CVP chemotherapy, administered every 3 weeks. MabThera/Rituxan IV was given at the standard dose of 375 mg/m^2. MabThera SC was given at a fixed dose of 1400 mg. Patients achieving at least partial response (PR) at the end of induction treatment were entered on to MabThera/Rituxan SC maintenance therapy administered once every 8 weeks for 24 months.
- MabThera IV arm (n=205): 8 cycles of MabThera IV in combination with up to 8 cycles of CHOP or CVP chemotherapy administered every 3 weeks. MabThera/Rituxan IV was given at the standard dose of 375 mg/m^2. Patients achieving at least at the end of induction were entered on to MabThera/Rituxan IV maintenance therapy administered once every 8 weeks for 24 months.

Overall response rate (ORR, comprising complete response [CR], unconfirmed response [CRu], and partial response [PR]) at the end of induction treatment was calculated using investigator assessment of response in the ITT population based on pooled data from Stages 1 and 2. Additionally, ORR and complete response rate (CRR, comprising CR and CRu) at the end of maintenance treatment and time-to-event endpoints (progression-free survival [PFS] and overall survival [OS]) were analyzed. Efficacy results are presented in Table 9 based on a median observation time of approximately 37 months.

Table 9 Efficacy Results for Study SABRINA/BO22334

	MabThera/Rituxan SC n=205	**MabThera/Rituxan IV** n=205
Overall Response Rate at End of Induction[a]		
Number of responders (CR/CRu, PR)	173	174
Overall response (CR/CRu, PR) rate (%, [95% CI])	84.4% [78.7;89.1]	84.9% [79.2;89.5]
Number of complete responders (CR/CRu)	66	66
Complete response (CR/CRu) rate (%, [95% CI])	32.2% [25.9;39.1]	32.2% [25.9;39.1]
Overall Response Rate at End of Maintenance		
Number of patients treated in maintenance (n)	172	178
Number of responders (CR/CRu, PR)	134	139
Overall response (CR/CRu, PR) rate (%, [95% CI])	77.9% [71.0;83.9]	78.1% [71.3;83.9]
Number of complete responders (CR/CRu)	87	100
Complete response (CR/CRu) rate (%, [95% CI])	50.6% [42.9;58.3]	56.2% [48.6;63.6]
Progression-free survival		
Number of patients with event	50 (24.4%)	57 (27.8%)
Hazard Ratio [95% CI] (unstratified Cox model)	0.84 [0.57;1.23]	
Overall survival		
Number of patients with event	16 (7.8%)	20 (9.8%)
Hazard Ratio [95% CI] (unstratified Cox model)	0.81 [0.42;1.57]	

[a] Stage 2 primary efficacy endpoint was ORR at the end of induction, however pooled results which were preplanned are presented in this Table.
Response rates based on investigator assessment.
Response rates at end of maintenance based on patients who received at least one cycle of maintenance treatment (n).

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

3.1.3 IMMUNOGENICITY

Data from the subcutaneous formulation development program indicate that the formation of anti-rituximab antibodies (HACAs) after SC administration is comparable with that observed after IV administration. In the SABRINA study (BO22334) the incidence of treatment-induced/enhanced anti-rituximab antibodies in the SC group was low and similar to that observed in the IV group (1.5% IV vs. 2% SC). The incidence of treatment-induced/enhanced anti-rHuPH20 antibodies was ~~6~~8% in the IV group compared with 13% in the SC group, and none of the patients who tested positive for anti-rHuPH20 antibodies tested positive for neutralizing antibodies. The overall proportion of patients found to have anti-rHuPH20 antibodies remained generally constant over the follow-up period in both cohorts.

The clinical relevance of the development of anti-rituximab or anti-rHuPH20 antibodies after treatment with MabThera SC is not known . There was no impact of the presence of anti-rituximab or anti-rHuPH20 antibodies on safety or efficacy in both studies.

3.2 Pharmacokinetic Properties

3.2.1 Absorption

Subcutaneous Formulation

SparkThera (BP22333):

MabThera at a fixed dose of 1400 mg was administered subcutaneously during maintenance, after at least one cycle of MabThera IV at a dose of 375 mg/m^2, in FL patients who had previously responded to MabThera IV in induction. The predicted median Cmax for the every two months regimen (q2m) for MabThera SC and the q2m regimen for. Similarly the every three months regimen (q3m) for MabThera SC and the q3m regimen for MabThera/Rituxan IV–the predicted median Cmax were comparable at 189 184 µg/mL, respectively. The median Ttmax in the MabThera SC group was approximately 3 days as compared to the Ttmax occuring at or close to the end of the infusion for the MabThera IV group.

SABRINA (BO22334):

MabThera at a fixed dose of 1400 mg was administered subcutaneously for 6 cycles during induction at 3-weekly intervals, following a first cycle of MabThera IV at a dose of 375 mg/m^2, in previously untreated FL patients in combination with chemotherapy. The serum MabThera Cmax at Cycle 7 was similar between the two treatment arms, with geometric mean (CV%) values of 250.63 (19.01) µg/mL and 236.82 (29.41) µg/mL for MabThera IV and MabThera SC, respectively with the resulting geometric mean ratio (Cmax, SC/Cmax, IV) of 0.941 (90% CI: 0.872, 1.015). Based on a population pharmacokinetic analysis, an absolute bioavailability of 71% (95%CI: 70.0 – 72.1) was estimated.

3.2.2 Distribution

Non-Hodgkin's Lymphoma

Intravenous Formulation

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

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

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

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

Subcutaneous Formulation

SparkThera (BP22333)

MabThera at a fixed dose of 1400 mg was administered subcutaneously during maintenance, after at least one cycle of MabThera IV at a dose of 375 mg/m^2, in FL patients who had previously responded IV, in FL patients who had previously responded to MabThera IV in induction. The predicted mean and geometric mean C_{trough} values at Cycle 2 were higher in the MabThera SC group than the MabThera IV group. The geometric mean values for the q2m regimen for MabThera SC and the q2m regimen for MabThera IV were 32.2 and 25.9 µg/, respectively and the q3m regimen for MabThera SC and the q3m regimen for MabThera IV were 12.1 and 10.9 µg/mL,

respectively. Similarly, the predicted mean and geometric mean AUCtau values at Cycle 2 were higher in the MabThera SC group compared with the MabThera IV group. The geometric mean for the q2m regimen for MabThera SC and the q2m regimen for MabThera IV were 5430 and 4012 µg•day/mL, respectively and the q3m regimen for MabThera/Rituxan SC and the q3m regimen for MabThera IV were 5320 and 3947 µg•day/mL, respectively.

SABRINA (BO22334)

MabThera at a fixed dose of 1400 mg was administered as a subcutaneous injection, in the abdomen, at 3-weekly intervals. Previously untreated patients with CD20+ FL Grade 1, 2, or 3a were randomized 1:1 to receive MabThera SC (first cycle MabThera IV at a dose of 375 mg/m^2 followed by 7 cycles of MabThera SC) or MabThera IV at a dose of 375 mg/m^2 (for 8 cycles) in combination with up to 8 cycles of CHOP or CVP chemotherapy administered every three weeks as part of induction treatment. The mean and geometric mean C_{trough} values at induction Cycle 7 (pre-dose Cycle 8) were higher among the MabThera SC group compared with the MabThera IV group. The geometric mean was 134.6 µg /mL for the MabThera SC group compared with 83.1 µg/mL for the MabThera IV group.

Similarly, the mean and geometric mean AUC values at induction Cycle 7 (pre-dose Cycle 8) were higher among the MabThera SC group than the MabThera IV group. The geometric mean AUC was 3778.9 µg•day/mL for the MabThera SC group compared with 2734.2 µg•day/mL for the r MabThera IV group.

In a population pharmacokinetic analysis in FL patients who received single or multiple infusions of MabThera IV as a single agent or in combination with chemotherapy, the population estimates of nonspecific clearance (CL1), initial specific clearance (CL2) (likely contributed by B cells or tumour burden) and central compartment volume of distribution (V1) were 0.194 L/day, 0.535 L/day, and 4.37 L, respectively. The estimated median terminal elimination half-life of MabThera SC was 29.7 days (range, 9.9 to 91.2 days).

In the final analysis dataset from 403 patients administered MabThera SC and/or IV in Studies BP22333 (277 patients) and BO22334 (126 patients) the mean (range) weight and BSA were 74.4 kg (43.9 to 130 kg) and 1.83 m2 (1.34 to 2.48 m2), respectively. Mean (range) age was 57.4 years (23 to 87 years). There were no differences between demographic and laboratory parameters for the two studies. However, the baseline B-cell counts were markedly lower in Study BP22333, than in Study BO22334, as patients in Study BP22333 entered the study having received a minimum of four cycles of MabThera IV in induction and at least one cycle of MabThera IV maintenance, whereas patients in Study BO22334 had not received MabThera prior to study enrollment. Data on baseline tumour load was available only for patients in Study BO22334.

BSA was identified as the main covariate. All clearance and volume parameters increased with the body size. Among other covariate dependencies, central volume increased with age and the absorption rate constant decreased with age (for patients aged > 60 years), but these age dependencies were shown to result in negligible changes in ~~R~~rituximab exposure. Anti-drug antibodies were detected in only 13 patients and did not result in any clinically relevant increase in clearance.

Chronic Lymphocytic Leukaemia

Intravenous Formulation

MabThera was administered as an i.v infusion at a first-cycle dose of 375 mg/m^2 increased to 500 mg/m^2 each cycle for 5 doses in combination with fludarabine and cyclophosphamide in CLL patients. The mean C_{max} ($\underline{n}$ =15) was 408 µg/mL (range, 97-764 µg/mL) after the fifth 500 mg/m^2 infusion.

Rheumatoid Arthritis

Following two intravenous infusions of rituximab at a dose of 1000 mg, two weeks apart, the mean terminal half-life was 20.8 days (range, 8.58 to 35.9 days), mean systemic clearance was 0.23 L/day (range, 0.091 to 0.67 L/day), and mean steady-state distribution volume was 4.6 L (range, 1.7 to 7.51 L). Population pharmacokinetic analysis of the same data gave similar mean values for systemic clearance and half-life, 0.26 L/day and 20.4 days, respectively. Population pharmacokinetic analysis revealed that BSA and gender were the most significant covariates to explain inter-individual variability in pharmacokinetic parameters. After adjusting for BSA, male subjects had a larger volume of distribution and a faster clearance than female subjects. The gender- related pharmacokinetic differences are not considered to be clinically relevant and dose adjustment is not required.

The pharmacokinetics of rituximab were assessed following two IV doses of 500 mg and 1000 mg on Days 1 and 15 in four studies. In all these studies, rituximab pharmacokinetics were dose proportional over the limited dose range studied. Mean C_{max} for serum rituximab following first infusion ranged from 157 to 171 µg/mL for 2 x 500 mg dose and ranged from 298 to 341 µg/mL for 2 x 1000 mg dose. Following second infusion, mean C_{max} ranged from 183 to 198 µg/mL for the 2 × 500 mg dose and ranged from 355 to 404 µg/mL for the 2 × 1000 mg dose. Mean terminal elimination half-life ranged from 15 to 16.5 days for the 2 x 500 mg dose group and 17 to 21 days for the 2 × 1000 mg dose group. Mean C_{max} was 16 to 19% higher following second infusion compared to the first infusion for both doses.

The pharmacokinetics of rituximab were assessed following two IV doses of 500 mg and 1000 mg upon re-treatment in the second course. Mean C_{max} for serum rituximab following first infusion was 170 to 175 µg/mL for 2 x 500 mg dose and 317 to 370 µg/mL for 2 x 1000 mg dose. C_{max} following second infusion, was 207 µg/mL for the 2 x 500 mg dose and ranged from 377 to 386 µg/mL for the 2 x 1000 mg dose. Mean terminal elimination half-life after the second infusion, following the second course, was 19 days for 2 x 500 mg dose and ranged from 21 to 22 days for the 2 x 1000 mg dose. PK parameters for rituximab were comparable over the two treatment courses. The pharmacokinetic parameters in the anti-TNF inadequate responder population, following the same dosage regimen (2 x 1000 mg, i.v., 2 weeks apart), were similar with a mean maximum serum concentration of 369 µg/mL and a mean terminal half-life of 19.2 days.

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

Based on the population pharmacokinetic analysis of data in 97 GPA and MPA patients who received 375 mg/m^2 MabThera IV once weekly for four doses, the estimated median terminal elimination half-life was 23 days (range, 9 to 49 days). Rituximab mean clearance and volume of distribution were 0.313 L/day (range, 0.116 to 0.726 L/day) and 4.50 L (range 2.2w5 to 7.39 L), respectively. The PK parameters of rituximab in GPA and MPA patients appear similar to what has been observed in RA patients (*see section 3.2 Pharmacokinetic Properties, Distribution*).

3.2.3 Elimination

See section 3.2.2 Distribution.

3.2.4 Pharmacokinetics in Special Populations

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

3.3 PRECLINICAL SAFETY

3.3.1 Other

Subcutaneous Formulation

The subcutaneous formulation contains recombinant human hyaluronidase (rHuPH20), an enzyme used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously. Systemic absorption of rHuPH20 after subcutaneous administration is unlikely to occur. However, pharmacokinetic and toxicology studies in animals demonstrate reductions in foetal weight and increases in the number of resorptions following injection of rHuPH20, at maternal systemic exposure levels comparable to those that could occur after accidental bolus IV administration of a single vial of the MabThera SC formulation in humans, based on the most conservative assumptions possible. There is no evidence of dysmorphogenesis (i.e. teratogenesis) resulting from systemic exposure to rHuPH20.

4 PHARMACEUTICAL PARTICULARS

4.1 List of Excipients

Recomninant human hyaluronidase (rHuPH20), L-histidine, L-histidine hydrochloride monohydrate, α,α-trehalose dehydrate, L-methionine, Polysorbate 80, Water for Injection (WFI)

4.2 Storage

Intravenous and Subcutaneous Formulation

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

Subcutaneous Formulation

Store in a refrigerator (2°C-8°C). Do not freeze. Keep the container in the outer carton in order to protect from light.

From a microbiological point of view, the product should be used immediately. If not used immediately, preparation should take place in controlled and validated aseptic conditions. In-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 48 hours at 2°C - 8°C and subsequent 8 hours at 30°C in diffused daylight.

4.3 Special Instructions for Use, Handling and Disposal

MabThera SC solution (once transferred from the vial into the syringe) is physically and chemically stable for 48 hours at 2°C - 8°C and subsequent 8 hours at 30°C in diffused daylight.

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

Incompatibilities

No incompatibilities between MabThera SC and polypropylene or polycarbonate syringe material or stainless steel transfer and injection needles have been observed.

Disposal of unused/expired medicines

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed via wastewater and disposal through household waste should be avoided. Use established "collection systems", if available in your location

The following points should be strictly adhered to regarding the use and disposal of syringes and other medicinal sharps:

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

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

4.4 Packs

Subcutaneous Formulation

Vial of 1400mg/11.7ml 1

Medicine: keep out of reach of children

MYMabtheraSC0518/CDS30.0

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Roche

Made in Switzerland by
F.-Hoffmann-La Roche Ltd, Basel,
manufacturing site Kaiseraugst