Truxima® 10mg/ml Concentrate for solution for infusion

Rituximab
A biosimilar product of MabThera®

1. DESCRIPTION

1.1 Therapeutic / Pharmacologic Class of Drug
Antineoplastic agent
ATC Code: L01XC02

1.2 Type of Dosage Form
Concentrate for solution for infusion.

1.3 Route of Administration
Intravenous (IV) infusion.

1.4 Sterile / Radioactive Statement
Sterile.

1.5 Qualitative and Quantitative Composition
Active ingredient: rituximab
Truxima® is a clear, colorless liquid supplied in sterile, preservative-free, non-pyrogenic single-dose vial.
Single-dose vial. Vial contains 100mg/10mL or 500 mg/50 mL.
Excipients: Sodium citrate, polysorbate 80, sodium chloride, water for injections.

2. CLINICAL PARTICULARS

2.1 Therapeutic Indication(s)

Non-Hodgkin's Lymphoma
Truxima® 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.

Chronic Lymphocytic Leukemia (CLL)
Truxima® is indicated, in combination with chemotherapy, for the treatment of patients with previously untreated and relapsed/refractory CD20-positive Chronic Lymphocytic Leukemia.

Granulomatosis with polyangiitis (Wegener's) (GPA) and Microscopic polyangiitis (MPA)
Truxima® in combination with glucocorticoids is indicated for the treatment of adult patients with severe, active Granulomatosis with polyangiitis (GPA, also known as Wegener's granulomatosis) and Microscopic polyangiitis (MPA).

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

Premedication and Prophylactic Medications
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 Truxima®.
Premedication with glucocorticoids should also be considered, particularly if Truxima® is not given in

combination with steroid-containing chemotherapy (see section 2.4 Warnings and Precautions).

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

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

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

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

Dosage adjustments during treatment:
No dose reductions of Truxima® are recommended. When Truxima® is given in combination with chemotherapy, standard dose reductions for the chemotherapeutic drugs should be applied.
Truxima® formulation is not intended for subcutaneous administration (see section 5.2 Special Instructions for Use, Handling and Disposal).
Do not administer the prepared infusion solutions as a push or bolus (see section 5.2 Special Instructions for Use, Handling and Disposal).

Intravenous Formulation Infusion Rate
First intravenous infusion:
The recommended initial infusion rate is 50 mg/hour; after the first 30 minutes, the rate can be escalated in 50 mg/hour increments every 30 minutes to a maximum of 400 mg/hour.

Subsequent intravenous infusions:
Subsequent infusions of Truxima® can be started at a rate of 100 mg/hour and increased by 100 mg/hour increments every 30 minutes to a maximum of 400 mg/hour.

Interchangeability
No interchangeability or substitution with a reference medicinal product is permitted.

Standard dosage
Low-grade or follicular non-Hodgkin's lymphoma
Initial treatment
- Intravenous monotherapy

The recommended dosage of Truxima® used as monotherapy for adult patients is 375 mg/m^2 body surface area (BSA), administered as an intravenous infusion (see "Intravenous Formulation Infusion Rate" sub-section, above) once weekly for 4 weeks.
The recommended dosage of Truxima® in combination with any chemotherapy is 375 mg/m^2 body surface area per cycle for a total of:
- 8 cycles R-IV with CVP (21 days/cycle)
- 8 cycles R-IV with MCP (28 days/cycle)
- 8 cycles R-IV with CHOP (21 days/cycle); 6 cycles if a complete remission is achieved after 4 cycles

- 6 cycles with R-CHVP-Interferon (21 days/cycle)
Truxima® should be administered on day 1 of each chemotherapy cycle after intravenous administration of the glucocorticoid component of the chemotherapy, if applicable.

Re-treatment following relapse
Patients who have responded to Truxima® initially may receive Truxima® at a dose of 375 mg/m^2 BSA, administered as an i.v. infusion once weekly for 4 weeks (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 Truxima® given at 375mg/m^2 once every 2 months until disease progression or for a maximum period of two years (12 infusions in total).
Relapsed/refractory patients after response induction treatment may receive maintenance therapy with Truxima® given at 375 mg/m^2 once every 3 months until disease progression or for a maximum period of two years (8 infusions in total).

Diffuse large B-cell non-Hodgkin's lymphoma
In patients with diffuse large B cell non-Hodgkin's lymphoma Truxima® should be used in combination with CHOP (cyclophosphamide, doxorubicin, prednisone and vincristine) chemotherapy. The recommended dosage of Truxima® is 375 mg/m^2 BSA, administered on day 1 of each chemotherapy cycle for 8 cycles after i.v. administration of the glucocorticoid component of CHOP (see "Intravenous Formulation Infusion Rate" sub-section, above).

Chronic Lymphocytic Leukemia
The recommended dosage of Truxima® in combination with chemotherapy for previously untreated and relapsed/refractory patients is 375 mg/m^2 body surface area administered on day 1 of the first treatment cycle followed by 500 mg/m^2 body surface area administered on day 1 of each subsequent cycle for 6 cycles in total (see section 3.1.2 Clinical / Efficacy Studies). The chemotherapy should be given after Truxima® infusion. (see "Intravenous Formulation Infusion Rate" sub-section, above).

Granulomatosis with polyangiitis (Wegener's) (GPA) and Microscopic polyangiitis (MPA)
The recommended dosage of Truxima® for treatment of GPA and MPA is 375 mg/m^2 body surface area, administered as an IV infusion (see "Intravenous Formulation Infusion Rate" sub-section, above) once weekly for 4 weeks.

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

Pneumocystis jiroveci pneumonia (PCP) prophylaxis is recommended for patients with GPA and MPA prior to and following Truxima® treatment, as appropriate according to local clinical practice guidelines.

2.2.1 Special Dosage Instructions
Children and adolescents:
The safety and effectiveness of rituximab in pediatric patients (<18 years) have not been established.
Geriatric use:
No dose adjustment is required in elderly patients (aged >65 years).

2.3 Contraindications
Truxima® is contraindicated in patients with known hypersensitivity to rituximab, to any component of the product or to murine proteins.

2.4 Warnings and Precautions

2.4.1 General

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

Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukemia Patients

Infusion-related reactions

Rituximab is associated with infusion-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.

Severe infusion-related reactions with fatal outcome have been reported during post-marketing use. Severe infusion-related reactions usually manifested within 30 minutes to 2 hours after starting the first rituximab 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 10^9/L) of circulating malignant cells such as patients with CLL and mantle cell lymphoma may be at higher risk of developing severe infusion-related reactions.

Infusion reaction symptoms are usually reversible with interruption of the infusion. Treatment of infusion-related symptoms with diphenhydramine and 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/h to 50 mg/h) when symptoms have completely resolved. Most patients who have experienced non-life threatening infusion-related reactions have been able to complete the full course of rituximab therapy. Further treatment of patients after complete resolution of signs and symptoms has rarely resulted in repeated severe infusion-related reactions.

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

Hypersensitivity Reactions / Anaphylaxis

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

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 infusion interrupted immediately (see section 2.2 Dosage and Administration) and should receive aggressive symptomatic treatment.

Rapid tumor lysis

Rituximab 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 rituximab 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 x 10^9/L) of circulating malignant cells such as patients with CLL. These patients should be followed closely and appropriate laboratory monitoring performed.

Appropriate medical therapy should be provided for patients who develop signs and symptoms consistent with

rapid tumour lysis. Following treatment for and complete resolution of signs and symptoms, subsequent rituximab therapy has been administered in conjunction with prophylactic therapy for TLS in a limited number of cases.

Cardiovascular

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

Monitoring of blood counts

Although rituximab is not myelosuppressive in monotherapy, caution should be exercised when considering treatment of patients with neutrophil counts of $<1.5 \times 10^9$/L and/or platelet counts of $<75 \times 10^9$/L, as clinical experience with such patients is limited. Rituximab 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 rituximab. When rituximab is given in combination with CHOP or CVP chemotherapy, regular full blood counts should be performed according to usual medical practice.

Infections

Rituximab 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 rituximab, 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 rituximab. At minimum this should include HBsAg-status and HBcAb-status. These can be complemented with other appropriate markers as per local guideline. Patients with active hepatitis B disease should not be treated with rituximab. 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 (PML)

Cases of progressive multifocal leukoencephalopathy (PML) have been reported during use of rituximab in CLL (see section 2.6 Undesirable Effects and 2.6.2. Post Marketing Experience). The majority of patients had received rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant. Physicians treating patients with 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 2.6.2 Post Marketing Experience). In case of such an event with a suspected relationship to rituximab, treatment should be permanently discontinued.

Immunization

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

Patients treated with rituximab 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 rituximab 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 rituximab.

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

The efficacy and safety of rituximab for the treatment of autoimmune disease other than rheumatoid arthritis, Granulomatosis with polyangiitis (Wegener's) and Microscopic polyangiitis has not been established.

Infusion-related Reactions

Rituximab 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 drug and an anti-histaminic drug, should always be administered before each infusion of rituximab. The most common infusion-related reactions for GPA and MPA patients were cytokine release syndrome, flushing, throat irritation, and tremor. (see section 2.6 Undesirable Effects, Granulomatosis with polyangiitis (Wegener's) and Microscopic polyangiitis). For GPA and MPA patients, rituximab 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.

Hypersensitivity Reactions /Anaphylaxis

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

Cardiovascular

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

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

Infections

Based on the mechanism of action of rituximab and the knowledge that B cells play an important role in maintaining normal immune response, patients may have an increased risk of infection following rituximab therapy. Rituximab 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 rituximab 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 rituximab 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 GPA and MPA patients receiving rituximab.

Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with rituximab. At minimum this should include HBsAg-status and HBcAb-status. These can be complemented with other appropriate markers as per local guideline. Patients with active hepatitis B disease should not be treated with rituximab. 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 2.6.2 Post Marketing Experience). In case of such an event, with a suspected relationship to rituximab, treatment should be permanently discontinued.

Progressive Multifocal Leukoencephalopathy

Cases of fatal progressive multifocal leukoencephalopathy have been reported following use of rituximab for the treatment of autoimmune diseases. 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 rituximab. 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 rituximab therapy has not been studied. Therefore vaccines with live virus vaccines is not recommended whilst on rituximab or whilst peripherally B cell depleted. Patients treated with rituximab may receive non-live vaccinations. However, response rates to non-live vaccines maybe reduced.

For patients treated with rituximab, physicians should review the patient's vaccination status and patients should, if possible, be brought up-to-date with all immunizations in agreement with current immunization guidelines prior to initiating rituximab therapy. Vaccinations should be completed at least 4 weeks prior to first administration of

rituximab.

2.4.2 Ability to Drive and Use Machines

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

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2.5 Fertility, pregnancy and lactation

Contraception in males and females

Due to the long retention time of rituximab in B cell depleted patients, women of childbearing potential should use effective contraceptive methods during and for 12 months after treatment with rituximab.

Pregnancy

IgG immunoglobulins are known to cross the placental barrier.
B cell levels in human neonates following maternal exposure to rituximab 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 rituximab should not be administered to pregnant women unless the possible benefit outweighs the potential risk.

Breast-feeding

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

Fertility

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

2.6 Undesirable Effects

2.6.1 Clinical Trials

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

Summary of the safety profile

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

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

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

The most frequently reported or observed serious adverse reactions were:

- IRRs (including cytokine-release syndrome, tumour-lysis syndrome), see section 2.4.
- Infections, see section 2.4.
- Cardiovascular events, see section 2.4.

Other serious ADRs reported include hepatitis B reactivation and PML (see section 2.4.).

Tabulated list of adverse reactions

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

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

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

MedDRA System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not known
Infections and infestations	bacterial infections, viral infections,	sepsis, [+]pneumonia, [+]febrile infection, [+]herpes zoster, [+]respiratory tract infection, fungal infections, infections of unknown aetiology		serious viral infection[2] Pneumocystis jirovecii	PML	
Blood and lymphatic system disorders	neutropenia, leucopenia	anaemia, thrombocytopenia	coagulation disorders, transient aplastic anaemia, haemolytic anaemia, lymphadenopathy		transient increase in serum IgM levels[3]	Late neutropenia[3]
Immune system disorders	angioedema	hypersensitivity		anaphylaxis	tumour lysis syndrome, cytokine release syndrome[4], serum sickness	infusion-related acute reversible thrombocytopenia[4]
Metabolism and nutrition disorders		hyperglycaemia, weight decrease, peripheral				

		edema, face edema, increased LDH, hypocalcemia				
Psychiatric disorders			depression, nervousness			
Nervous system disorders		paresthesia, hypoesthesia, agitation, insomnia, vasodilatation, dizziness, anxiety	dysgeusia		peripheral neuropathy, facial nerve palsy[5]	cranial neuropathy, loss of other senses[5]
Eye disorders		lacrimation disorder, conjunctivitis			severe vision loss[5]	
Ear and labyrinth disorders		tinnitus, ear pain				hearing loss[5]
Cardiac disorders		[+]myocardial infarction, arrhythmia, [+]atrial fibrillation, tachycardia, [+]cardiac disorder	[+]left ventricular failure, [+]supraventricular tachycardia, [+]ventricular tachycardia, [+]angina, [+]myocardial ischaemia, bradycardia	severe cardiac disorders[4 and 6]	heart failure[4 and 6]	
Vascular disorders		hypertension, orthostatic hypotension, hypotension			vasculitis (predominately cutaneous), leukocytoclastic vasculitis	
Respiratory, thoracic and mediastinal disorders		bronchospasm, respiratory disease, chest pain, dyspnoea, cough, rhinitis	asthma, bronchiolitis obliterans, lung disorder, hypoxia	interstitial lung disease[7]	respiratory failure[4]	lung infiltrati- on
Gastrointestinal disorders	nausea	vomiting, diarrhea, abdominal	abdominal enlargement		gastro-intestinal perforation[7]	

		pain, dysphagia, stomatitis, constipation dyspepsia, anorexia, throat irritation				
Skin and subcutaneous tissue disorders	pruritus, rash	urticaria , +alopecia, sweating, night sweats			severe bullous skin reactions, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome)[7]	
Musculoskeletal, connective tissue disorders		hypertonia, myalgia, arthralgia, back pain, neck pain, pain				
Renal and urinary disorders					renal failure[4]	
General disorders and administration site conditions	fever, chills, asthenia, headache	tumour pain, flushing, malaise, cold syndrome	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.

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

[2] see also section infection below

[3] see also section haematologic adverse reactions below

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

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

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

[7] includes fatal cases

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

Signs and symptoms suggestive of an infusion-related reaction were reported in more than 50% of patients in clinical trials, and were predominantly seen during the first infusion, usually in the first oneto two hours. These symptoms

mainly comprised fever, chills and rigors. Other symptoms included flushing, angioedema, bronchospasm, vomiting, nausea, urticaria/rash, fatigue, headache, throat irritation, rhinitis, pruritus, pain, tachycardia, hypertension, hypotension, dyspnoea, dyspepsia, asthenia and features of tumour lysis syndrome. Severe infusion-related reactions (such as bronchospasm, hypotension) occurred in up to 12% of the cases.

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

Description of selected adverse reactions

Infections

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

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

Haematologic adverse reactions

In clinical trials with rituximab monotherapy given for 4 weeks, haematological abnormalities occurred in a minority of patients and were usually mild and reversible. Severe (grade 3/4) neutropenia was reported in 4.2%, anaemia in 1.1% and thrombocytopenia in 1.7% of the patients. During rituximab maintenance treatment for up to 2 years, leucopenia (5% vs. 2%, grade 3/4) and neutropenia (10% vs. 4%, grade 3/4) were reported at a higher incidence when compared to observation. The incidence of thrombocytopenia was low (<1%, grade 3/4) and was not different between treatment arms. During the treatment course in studies with rituximab in combination with chemotherapy, grade 3/4 leucopenia (R-CHOP 88% vs. CHOP 79%, R-FC 23% vs. FC 12%), neutropenia (R-CVP 24% vs. CVP 14%; R-CHOP 97% vs.
CHOP 88%, R-FC 30% vs. FC 19% in previously untreated CLL), pancytopenia (R-FC 3% vs. FC 1% in previously untreated CLL) were usually reported with higher frequencies when compared to chemotherapy alone. However, the higher incidence of neutropenia in patients treated with rituximab and chemotherapy was not associated with a higher incidence of infections and infestations compared to patients treated with chemotherapy alone. Studies in previously untreated and relapsed/refractory CLL have established that in up to 25% of patients

treated with R-FC neutropenia was prolonged (defined as neutrophil count remaining below 1x109/L between day 24 and 42 after the last dose) or occurred with a late onset (defined as neutrophil count below 1x109/L later than 42 days after last dose in patients with no previous prolonged neutropenia or who recovered prior to day 42) following treatment with rituximab plus FC. There were no differences reported for the incidence of anaemia. Some cases of late neutropenia occurring more than four weeks after the last infusion of rituximab were reported. In the CLL first-line study, Binet stage C patients experienced more adverse events in the R-FC arm compared to the FC arm (R-FC 83% vs. FC 71%). In the relapsed/refractory CLL study grade 3/4 thrombocytopenia was reported in 11% of patients in the R-FC group compared to 9% of patients in the FC group.

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

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

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

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

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

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

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

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

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

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

Bulky disease

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

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

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

Experience from granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA)
Adult induction of remission (GPA/MPA Study 1)
In GPA/MPA Study 1, 99 adult patients were treated for induction of remission of GPA and MPA with rituximab (375 mg/m2, once weekly for 4 weeks) and glucocorticoids (see section 5.1).

The ADRs listed in Table 3 were all adverse events which occurred at an incidence of ≥ 5% in the rituximab group and at a higher frequency than the comparator group.

Table 2 Adverse reactions occurring at 6-months in ≥ 5% of adult patients receiving rituximab in GPA/MPA Study 1 (Rituximab n=99, at a higher frequency than the comparator group), or during post marketing surveillance.

MedDRA System organ class **Adverse reaction**	**Frequency**
Infections and infestations	
Urinary tract infection	7%
Bronchitis	5%

Herpes zoster	5%
Nasopharyngitis	5%
Serious viral infection[1]	not known
Blood and lymphatic system disorder	
Thrombocytopenia	7%
Immune system disorders	
Cytokine release syndrome	5%
Metabolism and nutrition disorders	
Hyperkalaemia	5%
Psychiatric disorders	
Insomnia	14%
Nervous system disorders	
Dizziness	10%

MedDRA System organ class **Adverse reaction**	**Frequency**
Infections and infestations	
Urinary tract infection	7%
Bronchitis	5%
Herpes zoster	5%
Nasopharyngitis	5%
Serious viral infection[1]	not known
Blood and lymphatic system disorder	
Thrombocytopenia	7%
Immune system disorders	
Cytokine release syndrome	5%
Metabolism and nutrition disorders	
Hyperkalaemia	5%
Psychiatric disorders	
Insomnia	14%
Nervous system disorders	
Dizziness	10%

MedDRA System organ class **Adverse reaction**	**Frequency**
Tremor	10%
Vascular disorders	
Hypertension	12%
Flushing	5%
Respiratory, thoracic and mediastinal disorders	
Cough	12%

Dyspnoea	11%
Epistaxis	11%
Nasal congestion	6%
Gastrointestinal disorders	
Diarrhoea	18%
Dyspepsia	6%
Constipation	5%
Skin and subcutaneous tissue disorders	
Acne	7%
Musculoskeletal and connective tissue disorders	
Muscle spasms	18%
Arthralgia	15%
Back pain	10%
Muscle weakness	5%
Musculoskeletal pain	5%
Pain in extremities	5%
General disorders and administration site conditions	
Peripheral oedema	16%
Investigations	
Decreased haemoglobin	6%

[1] Observed during post-marketing surveillance. See also section infections below.

Description of selected adverse reactions

Infusion-related reactions:
In GPA/MPA Study 1 (adult induction of remission study), IRRs 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. Of the 99 patients treated with rituximab, 12 (12%) experienced at least one IRR. All IRRs were CTC Grade 1 or 2. The most common IRRs included cytokine release syndrome, flushing, throat irritation, and tremor. Rituximab was given in combination with intravenous glucocorticoids which may reduce the incidence and severity of these events.

Infections:
In GPA/MPA Study 1, the overall rate of infection was approximately 237 per 100 patient years (95% CI 197 - 285) at the 6-month primary endpoint. Infections were predominately mild to moderate and consisted mostly of upper respiratory tract infections, herpes zoster and urinary tract infections. The rate of serious infections was approximately 25 per 100 patient years. The most frequently reported serious infection in the rituximab group was pneumonia at a frequency of 4%.

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

respiratory tract infection (2 patients [8%]) as the most frequently reported events.

In the post marketing setting, serious viral infections have been reported in GPA/MPA patients treated with rituximab.

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

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

atrial fibrillation (3%) (see section 4.4).

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

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

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

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

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

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

2.6.1.1 Laboratory Abnormalities

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

In the active controlled, randomized, double-blind, multicenter, non-inferiority study of rituximab in GPA and MPA, 24% of patients in the rituximab 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 rituximab-treated patients. The effect of multiple rituximab courses on the development of neutropenia in GPA and MPA patients has not been studied in clinical trials.

2.6.2 Post Marketing Experience

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 derived from spontaneous reports.

Additional cases of severe infusion-related reactions have been reported during post-marketing use of rituximab (see section 2.4 Warnings and Precautions).

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

Cardiovascular system:

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

Respiratory system:

Respiratory failure/insufficiency and lung infiltration in the context of infusion-related reactions (see section 2.4 Warnings and Precautions). In addition to pulmonary events associated with infusions, interstitial lung disease, some with fatal outcome, has 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 included visual disturbance, headache, seizures and altered mental status, with or without associated hypertension. A diagnosis of PRES/RPLS requires confirmation by brain imaging. The reported cases had recognized risk factors for PRES/RPLS, including the patients' underlying disease, hypertension, immunosuppressive therapy and/or chemotherapy.

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 rituximab therapy.

Body as a whole:

Serum sickness-like reactions have been reported rarely.

Infections and infestations:

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

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

Progression of Kaposi's sarcoma has been observed in rituximab-exposed patients with preexisting 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 rituximab in combination with chemotherapy for non-Hodgkin's lymphoma.
Granulomatosis with polyangiitis (Wegener's) (GPA) and Microscopic polyangiitis (MPA) patients
As part of the continuing post-marketing surveillance of rituximab safety, the following have been observed, or are 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:
Toxic Epidermal Necrolysis 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 infusion-related reactions some with fatal outcome have been reported (see section 2.6. Undesirable Effects, Clinical Trials).

2.6.2.1 Laboratory Abnormalities

Non-Hodgkin's Lymphoma
Blood and lymphatic system:
Neutropenia: Rarely the onset of neutropenia has occurred more than four weeks after the last infusion of rituximab.
In studies of rituximab 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

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

2.8 Interactions with other Medicinal Products and other Forms of Interaction

At present, there are limited data on possible drug interactions with rituximab.
In CLL patients, co-administration with rituximab 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 rituximab.
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.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 Pharmacodynamic Properties

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

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

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

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

Peripheral B-cell counts declined to levels below normal following the first dose of rituximab. In patients treated for hematological malignancies, B cell recovery began within 6 months of treatment and generally returning to normal level 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 GPA or MPA, the number of peripheral blood B cells decreased to <10 cells/μL after two weekly infusions of rituximab 375 mg/m2, and remained at that level in most patients up to the 6 month timepoint. The majority of patients (81%) showed signs of B cell return, with counts >10 cells/μL by month 12, increasing to 87% of patients by month 18.

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

Follicular lymphoma

Monotherapy

Initial treatment, weekly for 4 doses

In the pivotal study, 166 patients with relapsed or chemoresistant low-grade or follicular B-cell NHL received 375 mg/m^2 of rituximab as an IV infusion weekly for four doses. The overall response rate (ORR) in the intent-to-treat (ITT) population was 48% ($CI_{95\%}$ 41% - 56%) with a 6% complete response (CR) and a 42% partial response (PR) rate. The projected median time to progression (TTP) for responding patients was 13.0 months. In a subgroup analysis, the ORR was higher in patients with IWF B, C, and D histologic subtypes as compared to IWF A subtype (58% vs 12%), higher in patients whose largest lesion was <5 cm vs >7 cm in greatest diameter (53% vs 38%), and higher in patients with chemosensitive relapse as compared to chemoresistant (defined as duration of response <3 months) relapse (50% vs 22%). ORR in patients previously treated with autologous bone marrow transplant (ABMT) was 78% versus 43% in patients with no ABMT. Neither age, sex, lymphoma grade, initial diagnosis, presence or absence of bulky disease, normal or high LDH nor presence of extranodal disease had a statistically significant effect (Fisher's exact test) on response to rituximab. A statistically significant correlation was noted between response rates and bone marrow involvement. 40% of patients with bone marrow involvement responded compared to 59% of patients with no bone marrow involvement (p=0.0186). This finding was not supported by a stepwise logistic regression analysis in which the following factors were identified as prognostic factors: histologic type, bcl-2 positivity at baseline, resistance to last chemotherapy and bulky disease.

Initial treatment, weekly for 8 doses

In a multicenter, single-arm study, 37 patients with relapsed or chemoresistant, low grade or follicular B-cell NHL received 375 mg/m^2 of rituximab 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 rituximab 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 multicenter, 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 rituximab, were re-treated with 375 mg/m^2 of rituximab as IV infusion weekly for four doses. Three of the patients had received two courses of rituximab 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 rituximab (12.4 months).

Initial treatment, in combination with chemotherapy
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 rituximab 375 mg/m^2 in combination with CVP (R-CVP). Rituximab 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 rituximab in combination with chemotherapy regimen other than CVP (CHOP, MCP, CHVP/Interferon-α) have also demonstrated significant improvements in response rates, time-dependent parameters as well as in overall survival. Key results from all four studies are summarized in the table below.

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

Study	Treatment, n	Median FU, months	ORR, %	CR, %	Median TTF/PFS/EFS months	OS rates, %
M39021	CVP, 159	53	57	10	Median TTP: 14.7	53-months 71.1
	R-CVP, 162		81	41	33.6 $p < 0.0001$	80.9 $p = 0.029$
GLSG'00	CHOP, 205	18	90	17	Median TTF: 2.6 years	18-months 90

	R-CHOP, 223		96	20	Not reached p< 0.001	95 p = 0.016
OSHO-39	MCP, 96	47	75	25	Median PFS: 28.8	48-months 74
	R-MCP, 105		92	50	Not reached p < 0.0001	87 p = 0.0096
FL2000	CHVP-IFN, 183	42	85	49	Median EFS: 36	42-months 84
	R-CHVP-IFN, 175		94	76	Not reached p< 0.0001	91 p = 0.029

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

Maintenance therapy

Previously untreated follicular NHL

In a prospective, open label, international, multicenter, 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 rituximab maintenance therapy (n=505) or observation (n=513). The two treatment groups were all well balanced with regards to baseline characteristics and disease status. Rituximab maintenance treatment consisted of a single infusion of rituximab at 375mg/m^2 body surface area given every 2 months until disease progression or for a maximum period of two years.

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

Significant benefit from maintenance treatment with rituximab 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 4 below).

Data from extended follow-up of patients in the study (median follow-up 9 years) confirmed the long-term benefit of rituximab maintenance therapy in terms of PFS, EFS, TNLT and TNCT (see Table 4 below).

Table 4 Overview of efficacy results for maintenance rituximab vs. observation (25 and 9 years median follow-up final analysis)

	Primary Analysis (median FU: 25 months)		**Final Analysis (median FU: 9.0 years)**	
Efficacy Parameter	**Observation (N = 513)**	**Rituximab Maintenance (N = 505)**	**Observation (N = 513)**	**Rituximab Maintenance (N = 505)**
Primary efficacy				
Progression-free (median)	NR	NR	4.06 years	10.49 years
Long-rank p value	< 0.0001		< 0.0001	
Hazard ratio (95% CI)	0.89 (0.45, 1.74)		0.61 (0.52, 0.73)	
Risk reduction	50%		39%	
Secondary efficacy				
Overall Survival (median)	NR	NR	NR	NR
Long-rank p value	0.7246		0.7953	
Hazard ratio (95% CI)	0.89 (0.45, 1.74)		1.04 (0.77, 1.40)	
Risk reduction	11%		-6%	

Event-free survival (median)	38 months	NR	4.04 years	9.25 years
Long-rank p value	< 0.0001		< 0.0001	
Hazard ratio (95% CI)	0.54 (0.43, 0.69)		0.64 (0.54, 0.76)	
Risk reduction	46%		36%	
TNLT (median)	NR	NR	6.11 years	NR
Long-rank p value	0.0003		< 0.0001	
Hazard ratio (95% CI)	0.61 (0.46, 0.80)		0.66 (0.55, 0.78)	
Risk reduction	39%		34%	
TNCT (median)	NR	NR	9.32 yesars	NR
Long-rank p value	0.0011		0.0004	
Hazard ratio (95% CI)	0.60 (0.44, 0.82)		0.71 (0.59, 0.86)	
Risk reduction	40%		39%	
Overall response rate*	55%	74%	61%	79%
Chi-squared test p value	< 0.0001		< 0.0001	
Odds ration (95% CI)	2.33 (1.73, 3.15)		2.43 (1.84, 3.22)	
Complete response (CR/Cru) rate*	48%	67%	53%	67%
Chi-squared test p value	< 0.0001		< 0.0001	
Odds ration (95% CI)	2.21 (1.65, 2.94)		2.34 (1.80, 3.03)	

* at end of maintenance/observation; final analysis results based on median follow-up of 73 months.
FU: follow-up; NR" not reached at time of clinical cut off, TNCT: time to next chemotherapy treatment; TNLT: time to next antilymphoma treatment.

Rituximab maintenance treatment provided consistent benefit in all subgroups tested: gender (male, female), age (<60 years, ≥60 years), FLIP1 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). Exploratory analyses of the benefit of maintenance treatment showed a less pronounced effect in elderly patients (> 70 years of age), however sample sizes were small.

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

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

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

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

[1)] Estimates were calculated by hazard ratios
[2)] Last tumour response as assessed by the investigator. The "primary" statistical test for "response" was the trend test of CR

versus PR versus non-response ($p < 0.0001$)
Abbreviations: NA, not available, 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 randomisation. Maintenance treatment with rituximab 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 rituximab 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 rituximab maintenance treatment when compared to observation (95% Cl, 45%-72%). Kaplan-Meier estimated progression-free rates at 12 months were 78% in the rituximab maintenance group vs 57% in the observation group. An analysis of overall survival confirmed the significant benefit of rituximab maintenance over observation ($p=0.0039$ log-rank test). Rituximab maintenance treatment reduced the risk of death by 56% (95% Cl; 22%-75%).

Table 6 Maintenance phase: overview of efficacy results rituximab vs. observation (28 months median observation time)

Efficacy Parameter	Kaplan-Meier Estimate of Median Time to Event (Months)			Risk Reduction
	Observation (N = 167)	Rituximab (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 rituximab maintenance treatment was confirmed in all subgroups analysed, regardless of induction regimen (CHOP or R-CHOP) or quality of response to induction treatment (CR or PR) (see Table 6). Rituximab maintenance treatment significantly prolonged median PFS in patients responding to CHOP induction therapy (median PFS 37.5 months vs 11.6 months, $p<0.0001$) as well as in those responding to R-CHOP induction (median PFS 51.9 months vs 22.1 months, $p=0.0071$). Although subgroups were small, rituximab maintenance treatment provided a significant benefit in terms of overall survival for both patients responding to CHOP and patients responding to R-CHOP, although longer follow-up is required to confirm this observation.

Adult 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 rituximab 375 mg/m^2 plus CHOP (R-CHOP). Rituximab 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 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.

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

Chronic lymphocytic leukaemia
In two open-label randomized trials, a total of 817 previously untreated patients and 552 patients with relapsed/refractory CLL were randomized to receive either FC chemotherapy (fludarabine 25 mg/m^2, cyclophosphamide 250 mg/m^2, day 1-3) every 4 weeks for 6 cycles or rituximab in combination with FC (R-FC). Rituximab was administered at a dosage of 375 mg/m^2 during the first cycle one day prior to chemotherapy and at a dosage of 500 mg/m^2 on day 1 of each subsequent treatment cycle. A total of 810 patients (403 R-FC, 407 FC) the first line study (see Table 7a and Table 7b below) and 552 patients (276 R-FC, 276 FC) for the relapsed/refractory study (see Table 8) were analyzed for efficacy.

In the first-line study, after a median observation time of 48.1 months, the median PFS was 55 months in the R-FC group and 33 months in the FC group ($p < 0.0001$, log-rank test). The analysis of overall survival showed a significant benefit of R-FC treatment over FC chemotherapy alone ($p = 0.0319$, log-rank test) (Table 7a). The benefit in terms of PFS was consistently observed in most patient subgroups analysed according to disease risk at baseline (i.e. Binet stages A-C) (Table 7b).

Table 7a First-line treatment of chronic lymphocytic leukemia - overview of efficacy results for rituximab plus FC vs. FC alone (20.7 months median observation time)

Efficacy Parameter	Kaplan-Meier Estimate of Median Time to Event (Months)			Hazard Ratio
	FC (N = 407)	R-FC (N = 403)	Log-Rank p value	
Progression-free survival (PFS)	32.2 (32.8)***	39.8 (55.3)***	< 0.0001 (< 0.0001)***	0.56 (0.55)***
Overall Survival	NR (NR)***	NR (NR)***	0.0427 (0.0319)***	0.64 (0.73)***
Event Free Survival	31.1 (31.3)***	39.8 (51.8)***	< 0.0001 (<	0.55 (0.56)***

			0.0001)***	
Response rate (CR, nPR, or PR)	72.7%	86.1%	< 0.0001	n.a.
CR rates	17.2%	36.0%	<0.0001	n.a.
Duration of response*	34.7 (36.2)***	40.2 (57.3)***	0.0040 (< 0.0001)***	0.61 (0.56)***
Disease free survival (DFS)**	NR (48.9)***	NR (60.3)***	0.7882 (0.0520)***	0.93 (0.69)***
Time to new CLL treatment	NR (47.2)***	NR (69.7)***	0.0052 (< 0.0001)***	0.65 (0.58)***

Response rate and CR rates analysed using Chi-squared Test
*: only applicable to patients achieving a CR, nPR, PR
**: only applicable to patients achieving a CR

Table 7b First-line treatment of chronic lymphocytic leukemia Hazard ratios of progression-free survival according to Binet stage (ITT) – 48.1 months median observation time

Progression-free survival (PFS)	Number of patients		Hazard Ratio (95% CI)	Log-Rank p value
	FC	R-FC		
Binet Stage A	22	18	0.39 (0.15; 0.98)	0.0442
Binet Stage B	257	263	0.52 (0.41; 0.66)	< 0.0001
Binet Stage C	126	126	0.68 (0.49; 0.95)	0.0224

CI: Confidence Interval

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

Table 8 Treatment of relapsed/refractory chronic lymphocytic leukemia - overview of efficacy results for rituximab plus FC vs. FC alone (25.3 months median observation time)

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

Response rate and CR rates analysed using Chi-squared Test
NR: not reached n.a. not applicable
*: only applicable to patients with CR, nPR or PR as best overall response
**: only applicable to patients with CR as best overall response

Results from other supportive studies using rituximab in combination with other chemotherapy regimens (including CHOP, FCM, PC, PCM, bendamustine and cladribine) for the treatment of previously untreated and/or relapsed/refractory CLL patients have also demonstrated high overall response rates with benefit in terms

of PFS rates, albeit with modestly higher toxicity (especially myelotoxicity). These studies support the use of MabThera with any chemotherapy.

Data in approximately 180 patients pre-treated with rituximab have demonstrated clinical benefit (including CR) and are supportive for rituximab re-treatment.

Granulomatosis with polyangiitis (Wegener's) (GPA) and Microscopic polyangiitis (MPA):
A total of 197 patients with severely, active Granulomatosis with polyangiitis (Wegener's) (GPA) and Microscopic polyangiitis (MPA) were enrolled and treated in an active controlled, randomized, double-blind, multicenter, non-inferiority study. Patients were 15 years of age or older, diagnosed with severely, active Granulomatosis with polyangiitis (Wegener's) (75% of patients) or Microscopic Polyangiitis (MPA) (24% of patients) according to the Chapel Hill Consensus conference criteria (1% of patients had unknown GPA and MPA type).
Patients were randomized in a 1:1 ratio to receive either oral cyclophosphamide daily (2mg/kg/day) for 3-6 months, followed by azathioprine or rituximab (375 mg/ m^2) once weekly for 4 weeks. Patients in both arms received l000 mg of pulse intravenous (IV) methylprednisolone (or another equivalent-dose glucocorticoid) per day for 1 to 3 days, followed by oral prednisone (1 mg/kg/day, not exceeding 80 mg/day). Prednisone tapering was to be completed by 6 months from the start of study treatment.
The primary outcome measure was achievement of complete remission at 6 months defined as a Birmingham Vasculitis Activity Score for Wegener's Granulomatosis (BVAS/WG) of 0, and off glucocorticoid therapy. The prespecified non-inferiority margin for the treatment difference was 20%. The study demonstrated non-inferiority of rituximab to cyclophosphamide for complete remission at 6 months (see Table 9). In addition, the complete remission rate in the rituximab arm significantly greater than the estimated complete remission rate in patients with severe GPA and MPA not treated or treated only with glucocorticoids, based on historical control data.
Efficacy was observed both for patients with newly diagnosed GPA and MPA and for patients with relapsing disease.

Table 9 Percentage of Patients Who Achieved Complete Remission at 6 Months (Intent to Treat Population) [146]

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

CI: confidence interval
[a] Non-inferiority was demonstrated since the lower bound (-3.2%) was higher than the predetermined non-inferiority margin (-20%).
[b] The 95.1% confidence level reflects an additional 0.001 alpha to account for an interim efficacy

3.2 Pharmacokinetic Properties

3.2.1 Distribution

Non-Hodgkin's Lymphoma
Based on a population pharmacokinetic analysis in 298 NHL patients who received single or multiple infusions of rituximab as a single agent or in combination with CHOP therapy, the typical population estimates of nonspecific clearance (CL_1), specific clearance (CL_2) likely contributed by B cells or tumour burden, and central compartment volume of distribution (V_1) were 0.14 L/day, 0.59 L/day, and 2.7 L, respectively. The estimated median terminal elimination half-life of rituximab was 22 days (range, 6.1 to 52 days). Baseline CD19-positive cell counts and size of measurable tumour lesions contributed to some of the variability in CL_2 of rituximab in data from 161 patients given 375 mg/m^2 as an IV infusion for 4 weekly doses. Patients with higher CD19-positive cell counts or tumour lesions had a higher CL_2. However, a large component of inter-individual variability remained for CL_2 after correction for CD19-positive cell counts and tumour lesion size. V_1 varied by body surface area (BSA) and CHOP therapy. This variability in V_1 (27.1% and 19.0%) contributed by the range in BSA (1.53 to 2.32 m^2) and concurrent CHOP therapy, respectively, were relatively small. Age, gender, race, and WHO

performance status had no effect on the pharmacokinetics of rituximab. This analysis suggests that dose adjustment of rituximab with any of the tested covariates is not expected to result in a meaningful reduction in its pharmacokinetic variability.
Rituximab at a dose of 375 mg/m^2 was administered as an IV infusion at weekly intervals for 4 doses to 203 patients with NHL naïve 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.
Rituximab at a dose of 375 mg/m^2 was administered as an IV infusion at weekly intervals for 8 doses to 37 patients with NHL. The mean C_{max} increased with each successive infusion, spanning from a mean of 243 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 rituximab when administered as 6 infusions of 375 mg/m^2 in combination with 6 cycles of CHOP chemotherapy was similar to that seen with rituximab alone.
Chronic Lymphocytic Leukemia
Rituximab 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} (N=15) was 408 µg/mL (range, 97 - 764 µg/mL) after the fifth 500 mg/m^2 infusion.
Granulomatosis with polyangiitis (Wegener's) (GPA) and Microscopic polyangiitis (MPA)
The PK parameters in adult and pediatric patients with GPA/MPA receiving 375 mg/m^2 rituximab once weekly for four doses are summarized in Table 10.

Parameter	Statistic	Study Adult GPA/MPA
N	Number of Patients	97
Terminal Half-life (days)	Median (Range)	23 (9 to 49)
Clearance (L/day)	Mean (Range)	0.313 (0.116 to 0.726)
Volume of Distribution (L)	Mean (Range)	4.50 (2.25 to 7.39)

3.2.2 Elimination
See section 3.2.1 Distribution.
3.2.3 Pharmacokinetics in Special Populations
No pharmacokinetic data are available in patients with hepatic or renal impairment.

4. COMPARATIVE CLINICAL TRIALS
4.1 Comparative Trial Design and Study Demographics
Clinical studies conducted to support similarity between Truxima® and the reference biologic drug included:

- Study CT-P10 1.1 comparing Truxima® and MabThera® in patients with Rheumatoid Arthritis (RA) with PK similarity as the primary endpoint and additional PK attributes, PD, safety and efficacy as secondary endpoints over 72 weeks;
- Study CT-P10 1.3, an maintenance of study CT-P10 1.1, in which RA patients on MabThera® were switched to Truxima® and patients originally assigned to Truxima® remained on this treatment for further 2 treatment courses (up to 104 weeks from the first infusion of Core Study Period in Study CT-P10 1.1);
- Study CT-P10 3.2 comparing Truxima®, Rituxan®, and MabThera® in RA patients with 3-way PK similarity in Part 1 and therapeutic similarity in Part 2 as co-primary endpoint and additional PK, PD, efficacy and safety as secondary endpoints over 48 weeks (The main study period). In the extension

study period (up to 76 weeks for the entire study period) additional efficacy, safety and immunogenicity following a third course of treatment (Truxima® or Rituxan®) including a "single transition" from Rituxan®/MabThera® to Truxima®.

- Study CT-P10 3.3 comparing Truxima™ and Rituxan® in combination with cyclophosphamide, vincristine and prednisone (CVP) in patients with Advanced Follicular Lymphoma with PK similarity in Part 1 and non-inferiority of efficacy in Part 2 as co-primary endpoints and additional PK, PD, efficacy and safety as secondary endpoints over 8 cycles (24 weeks);
-

4.2 Comparative Study Results

4.2.1 Comparative Bioavailability Studies

Clinical study results of the major clinical studies, Studies CT-P10 1.1, 1.3, 3.2 and 3.3 are summarized based on which biosimilarity between Truxima® and Rituxan® / MabThera® was established.

4.2.1.1 Pharmacokinetics

Rheumatoid Arthritis

The PK analyses including primary and additional secondary PK parameters for Study CT-P10 1.1 were analyzed. The 90% CIs of the ratios of geometric LS means for all primary PK parameters (C_{max} and $AUC_{0\text{-}last}$) were entirely contained in the pre-defined equivalence margin of 80% to 125%. The results of these analyses are presented in Table 11.

Serum concentrations were also similar between the Truxima® and MabThera® groups.

Table 11 Analysis of Primary PK Endpoints ($AUC_{0\text{-}last}$ and C_{max}) of Truxima® and MabThera® (ANCOVA) in Study CT-P10 1.1 (Up to Week 24): All PK Population

Parameter	Treatment	Reference	N	Geometric LS Mean	Ratio (%) of Geometric LS Means	90% CI of Ratio (%)
Primary PK endpoints						
$AUC_{0\text{-}last}$ (day•µg/mL)	Truxima®	-	100	7812.11	96.30	88.03 - 105.34
	MabThera®	Roche (EU)	50	8112.53		
C_{max} (µg/mL)	Truxima®	-	100	468.62	95.23	89.27 - 101.59
	MabThera®	Roche (EU)	50	492.07		

Note: The log transformed PK endpoints were analyzed using an ANCOVA model with treatment as a fixed effect and region and prior anti-TNF-a blocker status as covariates.

ANCOVA: Analysis of covariance, $AUC_{0\text{-}last}$: Area under the serum concentration time curve from the start of the 1st infusion to the last measurable concentration after the 2nd infusion, CI: Confidence interval, C_{max}: Maximum serum concentration, LS: Least squares, PK: Pharmacokinetics

For the primary analysis, the 90% confidence intervals (CIs) of the ratios of geometric LS means for primary PK endpoints ($AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$ and C_{max}) were entirely contained in the equivalence margin of 80% to 125% indicating that rituximab exposure were similar in all 3 comparisons between 1) Truxima® and Rituxan®, 2) Truxima® and MabThera®, 3) Rituxan® and MabThera®. The results of these analyses are presented in Table 12.

Serum concentrations were also similar between the Truxima®, Rituxan® and MabThera® groups.

Table 12 Analysis of Primary PK Endpoints ($AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$ and C_{max}) of Truxima®, Rituxan® and MabThera® (ANCOVA) in Study CT-P10 3.2 (Part 1, Up to Week 24): PK Population

Parameter	Comparison	Treatment	Reference	N	Geometric LS Mean	Ratio (%) of Geometric LS Means	90% CI of Ratio (%)
Primary PK Endpoints							
$AUC_{0\text{-last}}$ (h•µg/mL)	Truxima® (Test) vs. Rituxan® (Reference)	Test	-	62	163216.09	101.84	91.77 - 113.01
		Reference	Roche (US)	63	160266.18		
	Truxima® (Test) vs. MabThera® (Reference)	Test	-	62	163216.09	94.08	84.63 - 104.58
		Reference	Roche (EU)	59	173484.71		
	MabThera® (Test) vs. Rituxan® (Reference)	Test	Roche (US)	59	173484.71	108.25	97.32 - 120.40
		Reference	Roche (EU)	63	160266.18		
$AUC_{0\text{-inf}}$ (h•µg/mL)	Truxima® (Test) vs. Rituxan® (Reference)	Test	-	59	163055.24	98.91	89.77 - 108.97
		Reference	Roche (US)	62	164855.33		
	Truxima® (Test) vs. MabThera® (Reference)	Test	-	59	163055.24	89.91	81.40 - 99.31
		Reference	Roche (EU)	56	181353.13		
	MabThera® (Test) vs. Rituxan® (Reference)	Test	Roche (EU)	56	181353.13	110.01	99.64 - 121.45
		Reference	Roche (US)	62	164855.33		
C_{max} (µg/mL)	Truxima® (Test) vs. Rituxan® (Reference)	Test	-	62	377.83	101.39	94.00 - 109.35
		Reference	Roche (US)	63	372.65		
	Truxima® (Test) vs. MabThera® (Reference)	Test	-	62	377.83	88.99	82.40 - 96.10
		Reference	Roche (EU)	59	424.57		
	MabThera® (Test) vs. Rituxan® (Reference)	Test	Roche (EU)	59	424.57	113.93	105.45 - 123.09
		Reference	Roche (US)	63	372.65		

ANCOVA: Analysis of covariance, $AUC_{0\text{-inf}}$: Area under the concentration-time curve from time 0 extrapolated to infinity over both doses of the 1st treatment course, $AUC_{0\text{-last}}$: Area under the concentration-time curve from time 0 to the last measurable concentration over both doses of the 1st treatment course, CI: Confidence interval, C_{max}: Observed maximum concentration after the 2nd infusion, LS: Least squares, PK: Pharmacokinetics

Non-Hodgkin's lymphoma

In study CT-P10 3.3 in patients with AFL administered 375mg/m^2 in combination with CVP (cyclophosphamide, vincristine, and prednisolone) regimen every 3 weeks, pharmacokinetics of Truxima® were found to be similar to those of Rituxan®. For the primary analysis, The 90% CIs of ratios of geometric LS means for both AUC_{tau} and $C_{max,ss}$ at Core Cycle 4 (12 weeks) were entirely within the equivalence range of 80% to 125% indicating that rituximab exposures from Truxim® were similar to those from Rituxan®. Up to Core Cycle 8 (24 weeks), the mean value of C_{max}, C_{trough} as secondary PK endpoints were similar between the Truxima® and Rituxan® groups.

Table 13 Analysis of AUC_{tau} and $C_{max,ss}$ of Truxima® and Rituxan® at Core Cycle 4 (ANCOVA) in Study CT-P10 3.3 (Part 1): PK Population

Parameter (Unit)	Treatment	Reference	N	Geometric LS Mean	Ratio (%) of Geometric LS Means	90% CI of the Ratio (%)
AUC_{tau} (h•µg/mL)	Truxima®	-	55	30650.83	95.31	81.01 - 112.13
	Rituxan®	Roche (US)	58	32159.74		
$C_{max,ss}$ (µg/mL)	Truxima®	-	55	225.88	101.38	93.49 - 109.94
	Rituxan®	Roche (US)	58	222.81		

ANCOVA: Analysis of covariance, AUC_{tau}: area under the serum concentration-time curve at steady state, $C_{max,ss}$: The observed maximum serum concentration following drug administration at steady state, CI: Confidence interval, LS: Least Squares, PK: Pharmacokinetics

4.2.1.2 Pharmacodynamics

B-cell kinetics were evaluated in all Truxima® studies. The pattern and extent of B-cell depletion were shown to be similar between the Truxima® and reference products (Rituxan® / MabThera®) groups (up to 104 weeks in Studies CT-P10 1.1 and CT-P10 1.3, up to 76 weeks in Study CT-P10 3.2, up to 24 weeks in study CT-P10 3.3).

Rheumatoid Arthritis

In Study CT-P10 1.1, B-cell counts decreased to below the LLoQ (20 cells/µL) immediately after the 1st infusion of the 1st treatment course (Core Study Period) for almost all patients and remained below this level for the majority of patients up to and including Week 32 of the 1st treatment course. In the 2nd treatment course (Extension Study Period), B-cell counts also decreased to below the LLoQ immediately after the 1st infusion of 2nd treatment course for almost all patients and remained below this level for the majority of patients until the end of the study.

In Study CT-P10 1.3, there were large decreases from baseline to Treatment 1 Week 24 in median B-cell counts in each treatment group at each time point, and those decreases were similar between the maintenance and switch groups.

In Study CT-P10 3.2, median B-cell counts decreased to below the LLoQ (20 cells/µL) immediately after the 1st infusion of the 1st treatment course and remained below this level up to Week 48 (Main Study Period) for Truxima®, Rituxan® and MabThera® groups. Overall, B-cell depletion showed similar trends among Truxima®, Rituxan® and MabThera® groups throughout the Main Study Period (up to Week 48). For the Extension Study Period, large decreases from baseline were observed in both mean and median values of B-cell counts in the Truxima® maintenance, Rituxan® maintenance, switched from Rituxan® and switched from MabThera® groups in all time points. The median B-cell counts remained below the LLoQ up to and including Extension Week 24 in all treatment groups. There was no difference in B-cell counts between switching to Truxima® from MabThera® and Rituxan® groups and the Truxima® and Rituxan® maintenance groups.

Non-Hodgkin's lymphoma

In Study CT-P10 3.3, the B-cell count decreased to the LLoQ (20 cells/µL) by 1 hour after the end of infusion at Core Cycle 1 and remained at the LLoQ at pre-dose at each subsequent cycle for the majority of patients up to and including Cycle 8 (over 24 weeks) in the Core Study Period. The extent of B-cell depletion was similar between Truxima® and Rituxan®.

4.2.2 Comparative Safety and Efficacy

4.2.2.1 Efficacy

Rheumatoid Arthritis

The efficacy of Truxima® in RA was demonstrated in three studies, CT-P10 3.2, 1.1 and 1.3 studies.

In Study CT-P10 3.2, the primary efficacy endpoint (the ANCOVA for the change from baseline in disease activity measured by DAS28 [CRP] at Week 24) demonstrated the therapeutic similarity between the Truxima® and reference products group (Rituxan® + MabThera®).

Table 14 Results of Primary Analysis of DAS28 (ANCOVA) at Week 24 in Study CT-P10 3.2: Efficacy population

Treatment Group	n	LS Mean (SE)	Estimate of Treatment Difference	90% CI of Treatment Difference
DAS28 (CRP)				
Truxima®	138	-2.11 (0.176)	-0.01	(-0.22, 0.20)
Rituxan® + MabThera®	196	-2.10 (0.178)		

Note: An analysis of covariance (ANCOVA) comparing the change from baseline of DAS28 at 24 weeks of treatment between two groups, Truxima® and Reference products (Rituxan® + MabThera®) considered the treatment as a fixed effect and Gender, Region (EU vs. non-EU), Race, study part, interaction of treatment group with study part, prior anti-TNF-α blocker status at baseline (intolerance case versus inadequate response), and RF or anti-CCP status at baseline (both positive versus both negative versus either RF or anti-CCP negative) as covariates.
ANCOVA: analysis of covariance, CI: confidence interval, CRP: C-reactive protein, DAS28: Disease Activity Score 28, ESR: erythrocyte sedimentation rate, LS: Least squares, SE: standard error, N': the number of subjects with an assessment

Non-Hodgkin's lymphoma

Study CT-P10 3.3 demonstrated therapeutic non-inferiority of Truxima® to Rituxan® in AFL patients as evaluated by ORR (CR + CRu + PR) according to 1999 IWG criteria over cycle 8. In the Intent-to-treat (ITT) population, the proportions of patients achieving overall response (CR + CRu + PR) were 95.7% (67/70) and 90.0% (63/70) in the Truxima™ and Rituxan® groups, respectively.

The difference in ORR between groups were 5.7% in the ITT population, and lies on the positive side of the pre-defined non-inferiority margin using a point estimate difference of -7% which was defined in the protocol based on reference product variability (Table 15).

Table 15 Proportion of Patients Achieving ORR (CR + CRu + PR) over Cycle 8 (24 weeks) According to the 1999 IWG Criteria in Study CT-P10 3.3 (Part 2): Intent-to-treat Population – Central Review (Best Overall Response)

Population Overall Response n/N (%)	Truxim®	Rituxan®	Difference [lower bound of 95% CI]
ITT Population			
ORR (CR + CRu + PR)	67/70 (95.7)	63/70 (90.0)	5.7% [-3.41%]
CR	21/70 (30.0)	15/70 (21.4)	-
CRu	6/70 (8.6)	8/70 (11.4)	-
PR	40/70 (57.1)	40/70 (57.1)	-

Note: ORR was calculated using Best Overall Response during induction period.
CR: Complete response, CRu: Unconfirmed complete response, ITT: Intent-to-treat, IWG: International working group, ORR: Overall response rate, PR: Partial response

4.2.2.2 Safety

The types, frequency and severity of adverse events were comparable between the biosimilar and the reference biologic drug.

Experience from Clinical Trials in Hemato-Oncology

The clinical safety data for Truxima® collected in an ongoing clinical trial in patients with advanced follicular lymphoma (AFL); Study CT-P10 3.3, demonstrated that there were no clinically meaningful differences between Truxima® and reference product Rituxan® in the populations studied. A total of 140 patients with AFL were exposed to Truxima® or Rituxan® and data up to Core Cycle 8 (24 weeks) is available.

During the Core Study Period, patients were treated with study drug (Truxima® or Rituxan®) in combination with cyclophosphamide, vincristine, prednisolone (CVP) for up to 8 cycles. On the 1st day of each 21-day (± 3 days) dosing cycle, patients received an IV infusion of either Truxima® or Rituxan® (375 mg/m^2 of body surface area

[BSA]). Listed in Table 16 are TEAEs reported for more than 5% of patients in either Truxima® or the reference product Rituxan® by preferred term of CT-P10 3.3 Core Study Period. The proportions of patients reporting TEAEs were similar between the treatment groups.

Table 16 Summary of TEAEs (Reported by more than 5% of Patients by PT in Either Treatment Group) in CT-P10 3.3: Safety Population

System Organ Class Preferred Term	**Truxima® (N=70)**	**Rituxan® (N=70)**	**Total (N=140)**
	Number (%) of Patients		
Number (%) of patients with ≥ 1 TEAE	**58 (82.9)**	**56 (80.0)**	**114 (81.4)**
Blood and lymphatic system disorders	**28 (40.0)**	**22 (31.4)**	**50 (35.7)**
Anaemia	5 (7.1)	4 (5.7)	9 (6.4)
Neutropenia	24 (34.3)	16 (22.9)	40 (28.6)
Gastrointestinal disorders	**27 (38.6)**	**27 (38.6)**	**54 (38.6)**
Abdominal pain	6 (8.6)	10 (14.3)	16 (11.4)
Constipation	12 (17.1)	9 (12.9)	21 (15.0)
Diarrhoea	4 (5.7)	5 (7.1)	9 (6.4)
Nausea	7 (10.0)	5 (7.1)	12 (8.6)
Stomatitis	1 (1.4)	4 (5.7)	5 (3.6)
General disorders and administration site conditions	**12 (17.1)**	**18 (25.7)**	**30 (21.4)**
Asthenia	3 (4.3)	6 (8.6)	9 (6.4)
Fatigue	4 (5.7)	6 (8.6)	10 (7.1)
Pyrexia	2 (2.9)	6 (8.6)	8 (5.7)
Infections and infestations	**22 (31.4)**	**26 (37.1)**	**48 (34.3)**
Lower respiratory tract infection	5 (7.1)	1 (1.4)	6 (4.3)
Pneumonia	5 (7.1)	1 (1.4)	6 (4.3)
Upper respiratory tract infection	5 (7.1)	12 (17.1)	17 (12.1)
Urinary tract infection	4 (5.7)	4 (5.7)	8 (5.7)
Injury, poisoning and procedural complications	**17 (24.3)**	**18 (25.7)**	**35 (25.0)**
Infusion related reaction	16 (22.9)	17 (24.3)	33 (23.6)
Metabolism and nutrition disorders	**6 (8.6)**	**13 (18.6)**	**19 (13.6)**
Decreased appetite	0	6 (8.6)	6 (4.3)
Hyperglycaemia	0	5 (7.1)	5 (3.6)
Musculoskeletal and connective tissue disorders	**17 (24.3)**	**16 (22.9)**	**33 (23.6)**
Arthralgia	4 (5.7)	4 (5.7)	8 (5.7)
Back pain	1 (1.4)	7 (10.0)	8 (5.7)

System Organ Class Preferred Term	Truxima® (N=70)	Rituxan® (N=70)	Total (N=140)
	Number (%) of Patients		
Myalgia	4 (5.7)	2 (2.9)	6 (4.3)
Nervous system disorders	**19 (27.1)**	**25 (35.7)**	**44 (31.4)**
Hypoaesthesia	5 (7.1)	0	5 (3.6)
Neuropathy peripheral	10 (14.3)	12 (17.1)	22 (15.7)
Paraesthesia	3 (4.3)	8 (11.4)	11 (7.9)
Psychiatric disorders	**2 (2.9)**	**8 (11.4)**	**10 (7.1)**
Insomnia	0	6 (8.6)	6 (4.3)
Skin and subcutaneous tissue disorders	**16 (22.9)**	**12 (17.1)**	**28 (20.0)**
Alopecia	10 (14.3)	5 (7.1)	15 (10.7)

TEAE: Treatment emergent adverse event

In Study CT-P10 3.3, a total of 114/140 (81.4%) patients experienced at least 1 TEAE; 58/70 (82.9%) and 56/70 (80.0%) patients in Truxima® and Rituxan® groups, respectively. Patients experiencing TEAEs across SOCs showed similar distribution between treatment groups. The TEAEs most frequently reported in the Truxima® and Rituxan® groups were neutropenia and infusion related reaction.

Experience from Rheumatoid Arthritis Clinical Trials

The clinical safety data for Truxima® collected in 3 clinical trials in patients with rheumatoid arthritis; Study CT-P10 1.1, 1.3, and 3.2, demonstrated that there were no clinically meaningful differences between Truxima® and reference products (Rituxan® and/or MabThera®) in the populations studied. A total of 525 patients with RA were exposed to Truxima®, Rituxan® or MabThera® up to 104 weeks throughout Studies CT-P10 1.1 and CT-P10 1.3, and up to 76 weeks in Study CT-P10 3.2, including 129 patients who were transitioned to Truxima® in the extension study period.

Patients received 2 x 1000 mg of Truxima® separated by a 2-week interval in each treatment course; in addition to methotrexate (7.5-25mg/week). All of the patients received premedication of an antipyretic (e.g. paracetamol), an antihistamine (e.g. chlorpheniramine) and/or a glucocorticoid (e.g. methylprednisolone) before each infusion of Truxima®. Listed in Table 5 are TEAEs reported for more than 5% of patients in either Truxima® or reference product group (Rituxan® + MabThera®) by preferred term in the pooled analysis of CT-P10 1.1 and CT-P10 3.2 Main Study Period. The proportions of patients reporting TEAEs were similar between the treatment groups.

Table 17 Summary of TEAEs reported for ≥ 5% of Patients by PT in Either Truxima® or Reference Product Group (Rituxan® + MabThera®) in the Pooled Analysis in Study CT-P10 1.1 and Study CT-P10 3.2 [Main Study Period]

System Organ Class Preferred Term	Truxima® (N=263)	Rituxan® + MabThera® (N=262)	Total (N=525)
	Number (%) of Patients		
Number (%) of patients with ≥ 1 TEAE	**198 (75.3)**	**179 (68.3)**	**377 (71.8)**
Infections and infestations	**101 (38.4)**	**92 (35.1)**	**193 (36.8)**
Lower respiratory tract infection	17 (6.5)	16 (6.1)	33 (6.3)
Upper respiratory tract infection	43 (16.3)	47 (17.9)	90 (17.1)
Urinary tract infection	27 (10.3)	14 (5.3)	41 (7.8)
Injury, poisoning and procedural complications	**59 (22.4)**	**43 (16.4)**	**102 (19.4)**

Infusion related reaction	45 (17.1)	28 (10.7)	73 (13.9)
Nervous system disorders	**26 (9.9)**	**24 (9.2)**	**50 (9.5)**
Headache	14 (5.3)	15 (5.7)	29 (5.5)

PT: Preferred term, RA: Rheumatoid arthritis, TEAE: Treatment emergent adverse event

The TEAEs most frequently reported in the Truxima® and the combined reference products group (Rituxan® + MabThera®), respectively, included upper respiratory tract infection, IRR and urinary tract infection. Although the proportion of patients who experienced at least 1 related TEAE of urinary tract infection in the Truxima® group was higher than that of the reference products group, there was no meaningful difference in the study drug related TEAE between the treatment groups (12/263 [4.6%] and 9/262 [3.4%] patients, respectively).
During the Extension Study Period in Study CT-P10 3.2, a total of 105/295 (35.6%) patients experienced at least 1 TEAE. The proportion of patients who experienced at least 1 TEAE were similar between the treatment groups: 48/122 (39.3%), 21/64 (32.8%), 26/62 (41.9%) and 10/47 (21.3%) patients in the Truxima® maintenance, Rituxan® maintenance, Switched from Rituxan® and Switched from MabThera® groups, respectively.

Table 18 Summary of TEAEs (Reported by more than 5% of Patients by PT in Any Treatment Group) in Extension Study Period of Study CT-P10 3.2: Safety Population in the Extension Study Period Subset

System Organ Class Preferred Term	**Truxima® maintenance (N=122)**	**Rituxan® maintenance (N=64)**	**Switched from Rituxan® (N=62)**	**Switched from MabThera® (N=47)**	**Total (N=295)**
Number (%) of patients with ≥ 1 TEAE	**48 (39.3)**	**21 (32.8)**	**26 (41.9)**	**10 (21.3)**	**105 (35.6)**
Infections and infestations	**21 (17.2)**	**14 (21.9)**	**14 (22.6)**	**3 (6.4)**	**52 (17.6)**
Lower respiratory tract infection	1 (0.8)	3 (4.7)	2 (3.2)	2 (4.3)	8 (2.7)
Upper respiratory tract infection	10 (8.2)	10 (15.6)	8 (12.9)	0	28 (9.5)
Urinary tract infection	8 (6.6)	2 (3.1)	2 (3.2)	1 (2.1)	13 (4.4)

TEAE: Treatment emergent adverse event

The TEAEs most frequently reported in the Truxima® maintenance, Rituxan® maintenance, Switched from Rituxan® and Switched from MabThera® groups, respectively, included upper respiratory tract infection and urinary tract infection (Table 6).
In Study CT-P10 1.3, which is the extension of Study CT-P10 1.1, a total of 13/58 (22.4%) patients experienced at least 1 TEAEs. The proportion of patients who experienced at least 1 TEAEs were similar between the treatment groups: 9/38 (23.7%) and 4/20 (20.0%) patients in the Truxima® maintenance and Switched from MabThera® groups, respectively.

Table 19 Summary of TEAEs (Reported by more than 5% of Patients by PT in Either Treatment Group) in Study CT-P10 1.3: Safety Population (Patients Who Received Study Drug in the Maintenance Study Period)

System Organ Class Preferred Term	**Truxima® Maintenance (N=38)**	**Switched from MabThera® (N=20)**	**Total (N=58)**
	Number (%) of Patients		
Number (%) of patients with ≥ 1 TEAE	**9 (23.7)**	**4 (20.0)**	**13 (22.4)**
Infections and infestations	**3 (7.9)**	**2 (10.0)**	**5 (8.6)**

System Organ Class Preferred Term	Truxima® Maintenance (N=38)	Switched from MabThera® (N=20)	Total (N=58)
	Number (%) of Patients		
Upper respiratory tract infection	2 (5.3)	1 (5.0)	3 (5.2)
Urinary tract infection	2 (5.3)	1 (5.0)	3 (5.2)

TEAE: Treatment emergent adverse event

The TEAEs that were reported in more than 5% of patients in any treatment group were upper respiratory tract infection and urinary tract infection. No other TEAEs were reported in more than 5% of patients in either treatment group (Table 18).

4.2.2.3 Immunogenicity

In Studies CT-P10 1.1 and CT-P10 1.3, the proportion of patients with positive ADA results was similar between the treatment groups: 18/95 (18.9%) patients and 9/46 (19.6%) at Core Week 24 and 12/58 (20.7%) patients and 5/20 (25.0%) patients at Extension Week 24 showed positive ADA results in the Truxima® and MabThera® groups, respectively.

In general, the incidence of ADA was similar between the Truxima® and MabThera® groups at baseline and probably during the initial period of the study. Furthermore, there was not an appreciable increase in proportion of ADA-positive patients following a 2nd treatment course. In general, the proportions of patients with positive ADA results were similar in the 2 treatment groups during the Study CT-P10 1.3 and there was no alteration in frequency of ADA following single transition from MabThera® to Truxima®.

In Study CT-P10 3.2 in RA patients, the proportion of patients with ADA positive results was generally comparable between the Truxima® and the reference products (MabThera® and Rituxan®) groups up to Week 48: 7/142 (4.9%) patients and 18/196 (9.2%) patients in the Truxima® and the reference products (MabThera® and Rituxan®) groups, respectively. No discernible changes in immunogenicity profile were observed following the single transition of treatment in the Extension Study Period. 16 out of 18 patients, who had at least 1 ADA positive result during the Extension Study Period, had at least 1 ADA positive test result during Main Study Period or at the baseline of Extension Study Period. Two patients (1 patient [1.6%] each in the Rituxan® maintenance group and switched from Rituxan® treatment group) had new positive ADA test results after Extension Week 0 infusion. In Study CT-P10 3.3 in AFL patients, the proportions of patients with positive results for ADA up to Core Cycle 8 (over 24 weeks) at post-treatment visits were similar between the 2 treatment groups: 3/70 (4.3%) patients and 2/70 (2.9%) patients in the Truxima® and Rituxan® groups, respectively.

Overall, the majority of patients had negative ADA test results at each time point in all Truxima® studies with both RA and AFL population.

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The proportions of patients with positive ADA results were similar between Truxima® and the reference products (MabThera® and/or Rituxan®) groups across the Truxima® studies.

Randomized clinical trials have not been conducted to compare MabThera® and Truxima® in patients with CLL, NHL other than follicular lymphoma, GPA and MPA. Clinical efficacy and safety have been conducted in selected indications (RA and advanced follicular lymphoma) to demonstrate clinical comparability between MabThera® and Truxima®. The extrapolation of these data to support uses of Truxima® in CLL, NHL, GPA and MPA is based on the demonstrated comparability, in terms of product quality, non-clinical, human pharmacokinetic and clinical characteristics.

5. PHARMACEUTICAL PARTICULARS

5.1 Storage

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

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

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

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

5.2 Special Instructions for Use, Handling and Disposal

Withdraw the required amount of Truxima® under aseptic conditions and dilute to a calculated Truxima® concentration of 1 - 4 mg/mL in an infusion bag containing sterile, non-pyrogenic 0.9%, aqueous saline solution or 5% aqueous dextrose solution. To mix the solution, gently invert the bag to avoid foaming. Parenteral medications should be inspected visually for particulate matter or discoloration prior to administration.

The prepared infusion solution of Truxima® is physically and chemically stable for 24 hours at 2°C - 8°C and subsequently 12 hours at room temperature.

Incompatibilities

No incompatibilities between rituximab and polyvinyl chloride or polyethylene bags or infusion sets 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

5.3 Packs

1 Vial of 10 ml (10mg/mL)
1 Vial of 50 ml (10 mg/mL)

Medicine: keep out of reach of children

Prepared on September 2023

Manufactured by CELLTRION, Inc. Incheon, Republic of Korea.