New Zealand Data Sheet

1. PRODUCT NAME

Truxima® Concentrate solution for intravenous infusion

(Rituximab 100 mg in 10 mL and 500 mg in 50 mL, Concentrate solution for intravenous infusion)

Truxima- is a biosimilar medicine.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient

Rituximab

Single dose vials containing 100 mg in 10 mL and 500 mg in 50 mL.

Each mL of concentrate contains 10 mg of rituximab.

Excipients

Sodium citrate dihydrate, polysorbate 80, sodium chloride, water for injections, hydrochloric acid or sodium hydroxide (pH adjusted to 6.5).

For the full list of excipients, see Section 6.1.

TRUXIMA® (rituximab) is a chimeric mouse/human monoclonal antibody that binds specifically to the transmembrane antigen CD20.

Truxima (rituximab) is produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology.

The prescribing physician should be involved in any decision regarding interchangeability (unless the product is known to be non-interchangeable). Additional information is available on the following website (www.medsafe.govt.nz/profs/RIss/Biosimilars.asp). Data comparing Truxima® to reference product (MabThera®) can be found under *Pharmacological properties* of this datasheet.

3. PHARMACEUTICAL FORM

Truxima® is a clear, colourless concentrate solution for intravenous infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Non-Hodgkin's lymphoma

Truxima® is indicated for the treatment of patients with:

- CD20 positive, previously untreated low-grade or follicular, B-cell non-Hodgkin's lymphoma in combination with chemotherapy,
- CD20 positive, relapsed or chemoresistant low-grade or follicular, B-cell non-Hodgkin's lymphoma.
- CD20 positive diffuse large B-cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) chemotherapy.

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

Chronic lymphocytic leukaemia

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

4.2 Dose and method of administration

General

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

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

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

Haematology

Low-grade or follicular non-Hodgkin's lymphoma

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

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

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

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

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

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

Re-treatment following relapse
Patients who have responded to Truxima® initially have been treated again with Truxima at a dose of 375 mg/m^2 body surface area, administered as an IV infusion once weekly for 4 weeks (see Pharmacological Properties, Pharmacodynamic Properties, 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 375 mg/m^2 body surface area once every 2 months until disease progression or for a maximum period of two years (12 infusions).

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

Diffuse large B-cell non-Hodgkin's lymphoma

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

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

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

Chronic lymphocytic leukaemia

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

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

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 a total of 6 cycles (see Clinical/Efficacy Studies). The chemotherapy should be given after the infusion of Truxima®.

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

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

First infusion
The recommended initial infusion rate is 50 mg/h; subsequently, the rate can be escalated by 50 mg/h

increments every 30 minutes to a maximum of 400 mg/h.

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

Dosage adjustments during treatment

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

Special Populations

Children and adolescents
The safety and effectiveness of rituximab in paediatric patients have not been established.

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

4.3 Contraindications

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

4.4 Special warnings and precaution for use

Truxima® is indicated for treatment of patients with:
Non-Hodgkin's lymphoma

Truxima is indicated for the treatment of patients with:

- CD20 positive, previously untreated low-grade or follicular, B-cell non-Hodgkin's lymphoma in combination with chemotherapy,
- CD20 positive, relapsed or chemoresistant low-grade or follicular, B-cell non-Hodgkin's lymphoma.
- CD20 positive diffuse large B-cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) chemotherapy.

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

Chronic lymphocytic leukaemia

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

and is **not indicated for use in other conditions**. (see Section 4.1 – THERAPEUTIC INDICATIONS).

This section also summarises information about rituximab in other conditions.

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

should be considered as clinically indicated.

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

If a diagnosis of PML is confirmed rituximab must be permanently discontinued. Patients should also be advised to inform their partner or caregivers about their treatment, since they may notice symptoms that the patient is not aware of.

Non-Hodgkin's lymphoma and chronic lymphocytic leukaemia patients

Infusion-related Reactions

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

Patients with a high number (> 25 x 10^9/L) of circulating malignant cells or high tumour burden such as patients with CLL and mantle cell lymphoma, who may be at higher risk of especially severe IRRs, should only be treated with extreme caution. These patients should be very closely monitored throughout the first infusion. Consideration should be given to the use of a reduced infusion rate for the first infusion in these patients, or a split dosing over two days during the first cycle and any subsequent cycles if the lymphocyte count is still > 25 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 dyspnoea. In some cases, symptoms worsened over time, while in others initial improvement was followed by clinical deterioration. Therefore, patients experiencing pulmonary events or other severe infusion-related symptoms should be closely monitored until complete resolution of their symptoms occurs. Patients with a history of pulmonary insufficiency or those with pulmonary tumour infiltration may be at greater risk of poor outcome and should be treated with increased caution. Acute respiratory failure may be accompanied by events such as pulmonary interstitial infiltration or oedema, visible on a chest x-ray. The syndrome usually manifests itself within 1 or 2 hours of initiating the first infusion. Patients who experience severe pulmonary events should have their infusion interrupted immediately (see Dose and method of administration) and should receive aggressive symptomatic treatment.

Rapid Tumour Lysis
Rituximab mediates the rapid lysis of benign and malignant CD20 positive cells. Signs and symptoms (e.g., hyperuricaemia, hyperkalaemia, hypocalcaemia, hyperphosphataemia, acute renal failure, elevated LDH) consistent with tumour lysis syndrome (TLS) have been reported to occur after the first 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 and mantle cell lymphoma). These patients should be followed closely and appropriate laboratory monitoring performed. Appropriate medical therapy should be provided for patients who develop signs and symptoms consistent with rapid tumour lysis. Following treatment for and complete resolution of signs and symptoms, subsequent 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, cardiac arrhythmia, such as atrial flutter and fibrillation, heart failure and 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 x 10^9/L and/or platelet counts of < 75 x 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 (HB) 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 a minimum this should include HB surface antigen status and anti-HB core antibody status. These can be complemented with other appropriate markers as per local guidelines. Patients with active HB disease should not be treated with rituximab. Patients with positive HB serology should consult a liver disease specialist before the start of treatment and should be monitored and managed according to guidelines to prevent HB reactivation.

Progressive Multifocal Leukoencephalopathy
Cases of progressive multifocal leukoencephalopathy (PML) have been reported during use of rituximab in NHL and CLL (see Undesirable effects and Post-marketing experience). The majority of patients had received rituximab in combination with chemotherapy or as part of a haematopoietic stem cell transplant. Physicians treating patients with NHL or CLL should consider PML in the differential diagnosis of patients reporting neurological symptoms and consultation with a Neurologist should be considered as clinically indicated.

Skin Reactions
Severe skin reactions such as toxic epidermal necrolysis and Stevens-Johnson syndrome, some with fatal

outcome, have been reported (see Post-marketing experience). If signs and symptoms suggestive of a severe skin reaction occur, with a suspected relationship to rituximab, treatment should be permanently discontinued.

Immunisation
The safety of immunisation with live viral vaccines following rituximab therapy has not been studies and vaccination with live viral 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-randomised 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 titre).

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

General

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

4.5 Interaction with other medicines and other forms of interaction

Truxima® is indicated for treatment of patients with:
Non-Hodgkin's lymphoma

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- CD20 positive, previously untreated low-grade or follicular, B-cell non-Hodgkin's lymphoma in combination with chemotherapy,
- CD20 positive, relapsed or chemoresistant low-grade or follicular, B-cell non-Hodgkin's lymphoma.
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Truxima® is indicated for maintenance treatment of patients with CD20 positive, low grade or follicular, B-cell non-Hodgkin's lymphoma.

Chronic lymphocytic leukaemia

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

and **is not indicated for use in other conditions**. (see Section 4.1 – THERAPEUTIC INDICATIONS).

This section also summarises information about rituximab in other conditions.

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

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

4.6 Fertility, pregnancy and lactation

Truxima® is indicated for treatment of patients with:
Non-Hodgkin's lymphoma

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This section also summarises information about rituximab in other conditions.

Pregnancy

IgG immunoglobulins are known to cross the placental barrier.

Developmental toxicity studies performed in cynomolgus monkeys revealed no evidence of embryotoxicity in utero. New born offspring of maternal animals exposed to rituximab were noted to have depleted B-cell populations during the post-natal phase.

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.

Contraception in males and females

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

Breastfeeding

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Truxima® is indicated for treatment of patients with:
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Clinical trials

Experience from clinical trials in haemato-oncology

The frequencies of adverse drug reactions (ADRs) reported with rituximab alone or in combination with chemotherapy are summarised in the tables below and are based on data from clinical trials. These ADRs had either occurred in single arm studies or had occurred with at least a 2% difference compared to the control arm in at least one of the major randomised clinical trials. ADRs are added to the appropriate category in the tables below according to the highest incidence seen in any of the major clinical trials. Within each frequency grouping ADRs are listed in descending order of severity. Frequencies are defined as very common ≥ 1/10 (≥ 10%), common ≥ 1/100 to < 1/10 (≥ 1% to < 10%) and uncommon ≥ 1/1,000 to < 1/100 (≥ 0.1% to < 1%).

Rituximab monotherapy/maintenance therapy
The ADRs in the table below are based on data from single-arm studies including 356 patients with low-grade or follicular lymphoma, treated with rituximab weekly as a single agent for the treatment or re-treatment of non-Hodgkin's lymphoma (see Clinical/efficacy studies). The table also contains ADRs based on data from 671 patients with follicular lymphoma who received rituximab as maintenance

therapy for up to 2 years following response to initial induction with CHOP, R-CHOP, R-CVP or R-FCM (see Clinical/efficacy studies). The ADRs were reported up to 12 months after treatment with monotherapy and up to 1 month after treatment with rituximab maintenance.

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

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

System Organ Class	Very Common (≥ 10%)	Common (≥ 1% - < 10%)	Uncommon (≥ 0.1% - < 1%)
disorders		abdominal pain, dysphagia, stomatitis, constipation dyspepsia, anorexia, throat irritation	enlargement
Skin and subcutaneous tissue disorders	pruritis, rash	urticaria, +alopecia, sweating, night sweats	
Musculoskeletal, connective tissue and bone disorders		hypertonia, myalgia, arthralgia, back pain, neck pain, pain	
General disorders and administration site conditions	fever, chills, asthenia, headache	tumour pain, flushing, malaise, cold syndrome	infusion site pain
Investigations	decreased IgG levels		

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

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

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

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

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

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

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

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

Further information on selected, serious adverse drug reactions

Infusion-related reactions (IRRs)

Monotherapy - 4 weeks treatment
Signs and symptoms suggestive of an IRR were reported in more than 50% of patients in clinical trials, and were predominantly seen during the first infusion. Hypotension, fever, chills, rigors, urticaria, bronchospasm, sensation of tongue or throat swelling (angioedema), nausea, fatigue, headache, pruritus, dyspnoea, rhinitis, vomiting, flushing, and pain at disease sites have occurred in association with rituximab infusion as part of an infusion-related symptom complex. Some features of tumour lysis syndrome have also been observed.

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

Infections

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

Maintenance Treatment (NHL) up to 2 years
Higher frequencies of infections overall, including Grade 3/4 infections, were observed during rituximab treatment. There was no cumulative toxicity in terms of infections reported over the 2-year maintenance period.

Data from clinical trials included cases of fatal PML in NHL patients that occurred after disease progression and retreatment (see Special warnings and precaution for use).

Combination Therapy (R-CVP in NHL; R-CHOP in DLBCL, R-FC in CLL)
In the R-CVP study no increase in the frequency of infections or infestations was observed. The most common infections were upper respiratory tract infections which were reported for 12.3% patients on R-CVP and 16.4% patients receiving CVP. Serious infections were reported in 4.3% of the patients receiving R-CVP and 4.4% of the patients receiving CVP. No life-threatening infections were reported during this study.

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

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

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

Haematologic Events

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

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

Combination Therapy (R-CVP in NHL; R-CHOP in DLBCL, R-FC in CLL)
During treatment with rituximab in combination with chemotherapy in clinical studies, Grade 3/4 leucopenia (R-CHOP 88% vs. CHOP 79%, R-FC 23% vs. FC 12%), neutropenia (R-CVP 24% vs. CVP 14%; R-CHOP 97% vs. CHOP 88%, R-FC 30% vs. FC 19% in previously untreated CLL), were usually reported with higher frequencies when compared to chemotherapy alone. However, the higher incidence of neutropenia in patients treated with 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 some cases neutropenia was prolonged or with a late onset following treatment in the rituximab plus FC group.

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

Cardiovascular Events

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

Maintenance Treatment (NHL) up to 2 years
The incidence of Grade 3/4 cardiac disorders was comparable between the two treatment groups. Cardiac events were reported as serious adverse events in < 1% of patients on observation and in 3% of patients on rituximab: atrial fibrillation (1%), myocardial infarction (1%), left ventricular failure (<1%), myocardial ischaemia (< 1%).

Combination Therapy (R-CVP in NHL; R-CHOP in DLBCL, R-FC in CLL)
In the R-CHOP study the incidence of Grade 3/4 cardiac arrhythmias, predominantly supraventricular arrhythmias such as tachycardia and atrial flutter/fibrillation, was higher in the R-CHOP group (6.9% of patients) as compared to the CHOP group (1.5% of patients). All of these arrhythmias either occurred in the context of a rituximab infusion or were associated with predisposing conditions such as fever, infection, acute myocardial infarction or pre-existing respiratory and cardiovascular disease (see Special

warnings and precaution for use). No difference between the R-CHOP and CHOP group was observed in the incidence of other Grade 3/4 cardiac events including heart failure, myocardial disease and manifestations of coronary artery disease.

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

IgG Levels

Maintenance Treatment (NHL) up to 2 years
After induction treatment, median IgG levels were below the lower limit of normal (LLN) (< 7 g/L) in both the observation and the rituximab groups. In the observation group, the median IgG level subsequently increased to above the LLN, but remained constant during rituximab treatment. 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).

Neurologic Events

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

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

Subpopulations

Elderly patients (≥ 65 years)
Monotherapy - 4 weeks treatment: The incidence of any ADR and of Grade 3/4 ADRs was similar in elderly and younger patients (88.3% vs 92.0% for any ADR and 16.0% vs 18.1% for Grade 3/4 ADRs).

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

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

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

Post-marketing experience

Non-Hodgkin's lymphoma and chronic lymphocytic leukaemia

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

Additional cases of severe infusion-related reactions have been reported during post-marketing use of rituximab (see Special warnings and precaution for use).

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.

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

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

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

- *Nervous system*: Cases of posterior reversible encephalopathy syndrome (PRES)/reversible posterior leukoencephalopathy syndrome (RPLS) have been reported. Signs and symptoms included visual disturbance, headache, seizures and altered mental status, with or without associated hypertension. A diagnosis of PRES/RPLS requires confirmation by brain imaging. The reported cases had recognised risk factors for PRES/RPLS, including the patients' underlying disease, hypertension, immunosuppressive therapy and/or chemotherapy. Cases of cranial neuropathy with or without peripheral neuropathy have been reported rarely. Signs and symptoms of cranial neuropathy, such as severe vision loss, hearing loss, loss of other senses and facial nerve palsy, occurred at various times up to several months after completion of 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 Special warnings and precaution for use).Other serious viral infections, either new, reactivation or exacerbation, some of which were fatal, have been reported with rituximab treatment. The majority of patients had received rituximab in combination with chemotherapy or as part of a haematopoietic stem cell transplant. Examples of these serious viral infections are infections caused by the herpes viruses (cytomegalovirus (CMV), Varicella zoster virus and Herpes simplex virus), JC virus (progressive multifocal leukoencephalopathy (PML) see Special warnings and precaution for use) and Hepatitis C virus. Progression of Kaposi's sarcoma has been observed in rituximab-exposed patients with pre-existing Kaposi's sarcoma. These cases occurred in non-approved indications and the majority of patients were HIV positive.

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

Information regarding adverse effects in RA patients from other rituximab products is summarised below.

Paediatric use

The safety and effectiveness of rituximab in paediatric patients have not been established. Hypogammaglobulinaemia has 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.

Comparability of Truxima® with MabThera®

Truxima® is indicated for treatment of patients with:
Non-Hodgkin's lymphoma

Truxima® is indicated for the treatment of patients with:

- CD20 positive, previously untreated low-grade or follicular, B-cell non-Hodgkin's lymphoma in combination with chemotherapy,
- CD20 positive, relapsed or chemoresistant low-grade or follicular, B-cell non-Hodgkin's lymphoma.
- CD20 positive diffuse large B-cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) chemotherapy.

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

Chronic lymphocytic leukaemia

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

and **is not indicated for use in other conditions**. (see Section 4.1 – THERAPEUTIC INDICATIONS).

In all clinical studies conducted, Truxima® was well tolerated, and the safety profile of Truxima® was similar to that of MabThera®

These studies provide a total safety database for Truxima® of 70 AFL patients exposed up to 6 months (24 weeks) from Study CT-P10 3.3.

There were no notable differences between the Truxima® and reference products (MabThera® and/or Rituxan®) groups across the studyand by NHL populations with regards to the proportion of patients with TEAEs, TESAEs, AESIs, and TEAEs leading to permanent study drug discontinuation.

The comparative analysis did not reveal any trends or new signals noted in the patients treated with Truxima.

The summary of TEAEs in and CT-P10 3.3 is presented in the following tables:

Table 3 Summary of TEAEs (Reported more than 3% of Patients by PT in Either Treatment Group) in CT-P10 3.3 (Part 2): Safety Population

System Organ Class Preferred Term	CT-P10 375 mg/m^2 (N=70)	Rituxan® 375 mg/m^2 (N=70)	Total (N=140)
	Number (%) of Patients		
Number (%) of patients with ≥ 1 related 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)

System Organ Class Preferred Term	CT-P10 375 mg/m^2 (N=70)	Rituxan® 375 mg/m^2 (N=70)	Total (N=140)
	Number (%) of Patients		
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)
Vomiting	3 (4.3)	0	3 (2.1)
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)
Oedema	3 (4.3)	2 (2.9)	5 (3.6)
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)
Sinusitis	3 (4.3)	1 (1.4)	4 (2.9)
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)
Investigations	**7 (10.0)**	**6 (8.6)**	**13 (9.3)**
Weight decreased	1 (1.4)	3 (4.3)	4 (2.9)
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)
Bone pain	1 (1.4)	3 (4.3)	4 (2.9)
Myalgia	4 (5.7)	2 (2.9)	6 (4.3)
Nervous system disorders	**19 (27.1)**	**25 (35.7)**	**44 (31.4)**
Headache	3 (4.3)	3 (4.3)	6 (4.3)
Hypoaesthesia	5 (7.1)	0	5 (3.6)
Neuropathy peripheral	10 (14.3)	12 (17.1)	22 (15.7)

System Organ Class Preferred Term	CT-P10 375 mg/m^2 (N=70)	Rituxan® 375 mg/m^2 (N=70)	Total (N=140)
	Number (%) of Patients		
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)
Respiratory, thoracic and mediastinal disorders	**8 (11.4)**	**9 (12.9)**	**17 (12.1)**
Cough	1 (1.4)	3 (4.3)	4 (2.9)
Dyspnoea	3 (4.3)	1 (1.4)	4 (2.9)
Oropharyngeal pain	0	3 (4.3)	3 (2.1)
Skin and subcutaneous tissue disorders	**16 (22.9)**	**12 (17.1)**	**28 (20.0)**
Alopecia	10 (14.3)	5 (7.1)	15 (10.7)
Rash	3 (4.3)	1 (1.4)	4 (2.9)
Vascular disorders	**6 (8.6)**	**4 (5.7)**	**10 (7.1)**
Hypertension	3 (4.3)	1 (1.4)	4 (2.9)
Thrombophlebitis	0	3 (4.3)	3 (2.1)

Note: Some Preferred Terms (PTs) were combined.

TEAE: Treatment emergent adverse event

Reporting of suspected adverse reactions

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

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Pharmacotherapeutic group: antineoplastic agents, monoclonal antibodies, ATC code: L01XC02.

Mechanism of action

Truxima® is indicated for treatment of patients with:
Non-Hodgkin's lymphoma

Truxima® is indicated for the treatment of patients with:

- CD20 positive, previously untreated low-grade or follicular, B-cell non-Hodgkin's lymphoma in combination with chemotherapy,
- CD20 positive, relapsed or chemoresistant low-grade or follicular, B-cell non-Hodgkin's lymphoma.
- CD20 positive diffuse large B-cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) chemotherapy.

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

Chronic lymphocytic leukaemia

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

and **is not indicated for use in other conditions**. (see Section 4.1 – THERAPEUTIC INDICATIONS).

This section also summarises information about rituximab in other conditions.

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

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

Peripheral B–cell counts declined to levels below normal following the first dose of rituximab. In patients treated for haematological malignancies, B-cell recovery began within 6 months of treatment and generally returning to normal levels within 12 months after completion of therapy, although in some patients this may take longer (see Undesirable effects - Experience from clinical trials in haemato-oncology).

Information regarding B-cells depletion in RA patients from other rituximab products is summarised below.

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

Comparability of Truxima® with MabThera®

As part of the pharmaceutical and nonclinical development programme of Truxima, 14 *in vitro* pharmacodynamic tests were conducted comparing Truxima to reference product MabThera®. *In vitro* similarity assays such as cell-based CD20, FcRn, FcγRI, FcγRIIa, FcγRIIb, FcγRIIIa (F type), FcγRIIIa (V type), FcγRIIIb, and C1q binding, and corresponding effects: apoptosis, ADCC, and CDC, have been performed to demonstrate similarity in the mechanism of action between Truxima and MabThera® The *in vitro* primary PD studies demonstrated an identical mechanism of action between Truxima and reference

products in terms of binding affinity to CD20, apoptosis, binding affinity to Fcγ receptors and FcRn, antibody-dependent cellular cytotoxicity (ADCC), C1q binding affinity and complement-dependent cytotoxicity (CDC).

Information regarding B-cells depletion in RA patients from other rituximab products is summarised below.

* CT-P10 is Truxima's project code.
** Rituxan® is the USA registered tradename of the reference product.

In Study CT-P10 3.3 in patients with AFL, the median B-cell count depleted immediately after Core Cycle 1 and consistent up to and including Cycle 8 (over 24 weeks) in the Core Study Period. It is considered that the extent of B-cell depletion effect is similar between Truxima and Rituxan®.

Clinical/efficacy studies

Comparability of Truxima® with MabThera®

The clinical comparability between Truxima and MabThera® in one randomized, controlled, parallel-group, double blind, multicenter study in AFL patients.

Advanced Follicular Lymphoma

Study CT-P10 3.3

A total number of 140 patients including 121 patients from Part 1 were randomised to receive either CT-P10 (N=70) or Rituxan® (N=70). All randomised patients in the CT-P10 and Rituxan® treatment groups initiated study treatment and the majority of patients completed the Core Study Period (62 [88.6%] patients in each group) except 16 patients (8 [11.4%] patients in each group, respectively) who early discontinued before completion of the Core Study Period. The most frequently reported reasons for discontinuation from the Core Study Period were progressive disease (2 [2.9%] patients and 3 [4.3%] patients in the CT-P10 and Rituxan® groups, respectively) and adverse event (4 [5.7%] patients and 1 [1.4%] patient in the CT-P10 and Rituxan® groups, respectively).

The primary efficacy endpoint for Study CT-P10 3.3 assessed in Part 2 of the study, ORR (CR + CRu + PR) according to 1999 IWG criteria over Cycle 8 in PP population is presented in the table below. The proportions of patients achieving ORR according to 1999 IWG criteria were 97.0% (64/66 patients) and 92.6% (63/68 patients) in the CT P10 and Rituxan® groups, respectively.

Table 3 Proportion of Patients Achieving ORR (CR + CRu + PR) over Cycle 8 (Week 24) of Core Study Period According to the 1999 IWG Criteria in Study CT-P10 3.3: Per-protocol Population - Independent Review

Number of patients (%)	CT-P10	Rituxan®	Difference (%) [1]
PP Population			
ORR (CR + CRu + PR)	64/66 (97.0)	63/68 (92.6)	(4.3)
CR	20/66 (30.3)	15/68 (22.1)	-
CRu	6/66 (9.1)	8/68 (11.8)	-
PR	38/66 (57.6)	40/68 (58.8)	-

[1] Difference was calculated using percentages not the round off values.
ORR: Overall response rate, CR: Complete response, CRu: Unconfirmed complete response, PR: Partial response

In Study CT-P10 3.3, efficacy in terms of overall response rate using the 1999 IWG criteria was evaluated

over 24 week period and efficacy was comparable between CT-P10 and Rituxan® group.

Clinical trials with MabThera®

Low-grade or follicular non-Hodgkin's lymphoma

Monotherapy
Initial treatment, weekly for 4 doses
In the pivotal study, 166 patients with relapsed or chemoresistant low-grade or follicular B–cell NHL received 375 mg/m^2 of rituximab as an IV infusion weekly for four doses. The overall response rate (ORR) in the intent-to-treat (ITT) population was 48% (CI95% 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 multi-centre, 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% (CI95% 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% (CI95% 21% – 51%; CR 3%, PR 33%) with a median TTP for responding patients of 9.6 months (range 4.5 to 26.8 months).

Re-treatment, weekly for 4 doses
In a multi-centre, single-arm study, 58 patients with relapsed or chemoresistant low grade or follicular B–cell NHL, who had achieved an objective clinical response to a prior course of 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 enrolment and thus were given a third course in the study.

Two patients were re-treated twice in the study. For the 60 re-treatments on study, the ORR was 38% (CI95% 26% – 51%; 10% CR, 28% PR) with a projected median TTP for responding patients of 17.8 months (range 5.4 – 26.6). This compares favourably with the TTP achieved after the prior course of rituximab (12.4 months).

In combination with chemotherapy
Initial treatment
In an open-label randomised trial, a total of 322 previously untreated patients with follicular lymphoma were randomised to receive either CVP chemotherapy (cyclophosphamide 750 mg/m^2, vincristine 1.4 mg/m^2 up to a maximum of 2 mg on day 1, and prednisolone 40 mg/m^2/day on days 1-5) every 3 weeks for 8 cycles or 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 analysed for efficacy.

The median follow-up of patients was 53 months. R-CVP led to a significant benefit over CVP for the primary endpoint, time to treatment failure (27 months vs. 6.6 months, p < 0.0001, log-rank test). The proportion of patients with a tumour response (CR, CRu, PR) was significantly higher (p<0.0001 Chi-Square test) in the R-CVP group (80.9%) than the CVP group (57.2%). Treatment with R-CVP significantly prolonged the time to disease progression or death compared to CVP, 33.6 months and 14.7 months, respectively (p<0.0001, log-rank test). The median duration of response was 37.7 months in the R-CVP group and was 13.5 months in the CVP group (p < 0.0001, log-rank test). The difference between the treatment groups with respect to overall survival showed a strong clinical benefit (p=0.029, log-rank test stratified by centre). Survival rates at 53 months were 80.9% for patients in the R-CVP group compared to 71.1% for patients in the CVP group.

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

Table 4 Summary of key results from four phase III randomised studies evaluating the benefit of rituximab with different chemotherapy regimens in follicular lymphoma

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

Abbreviations: ORR – overall response rate; CR – complete response; OS rates – overall survival rates at the time of the analyses; R – rituximab; CVP – cyclophosphamide, vincristine, prednisolone; CHOP - cyclophosphamide, doxorubicin, vincristine, prednisone; MCP – mitoxantrone, chlorambucil, prednisolone; CHVP - cyclophosphamide, doxorubicin, etoposide, prednisolone ; IFN – interferon-alfa 2a.
[1]M39021 outcome: TTP (time to progression or death); GLSG'00 outcome: TTF (time to treatment failure);OSHO-39: PFS (progression free survival); FL2000 outcome: EFS (event free survival).

Maintenance therapy - previously untreated follicular NHL
In a prospective, open label, international, multi-center, phase III trial 1193 patients with previously untreated advanced follicular lymphoma received induction therapy with R-CHOP (n=881), R-CVP (n=268) or R-FCM (n=44), according to the investigators' choice. A total of 1078 patients responded to induction therapy, of which 1018 were randomised to rituximab maintenance therapy (n=505) or

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

After a median observation time of 25 months from randomisation, maintenance therapy with rituximab resulted in a clinically relevant and statistically significant improvement in the primary endpoint of investigator assessed progression-free survival (PFS) as compared to no maintenance therapy in patients with previously untreated follicular NHL (Table 6). This improvement in PFS was confirmed by an independent review committee (IRC).

Significant benefit from maintenance treatment with 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) (Table 6).

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

Table 5 Overview of efficacy results for maintenance rituximab vs. observation (25 and 73 months median observation time)

Efficacy Parameter	**Primary Analysis[a]**		**Updated Analysis[b]**	
	Observation N = 513	**Rituximab Maintenance N = 505**	**Observation N = 513**	**Rituximab Maintenance N = 505**
Primary Endpoint				
Progression-free Survival[c]				
Median time to event (months)	NR	NR	49	NR
p value (stratified log-rank test)	p = 0.0001		p = 0.0001	
HR [95% CI] (stratified)	0.50 [0.39;0.64]		0.58 [0.48; 0.69]	
Secondary Endpoints				
Overall Survival				
Median time to event (months)	NR	NR	NR	NR
p value (stratified log-rank test)	p = 0.7246		p = 0.8959	
HR [95% CI] (stratified)	0.89 [0.45;1.74]		1.02 [0.71; 1.47]	
Overall Response Rate at End of Maintenance/Observation				
Patients assessed at end of treatment	398	389	509	500
Responders (CR/Cru, PR)	219/398 (55%)	288/389 (74%)	309/509 (61%)	395/500 (79%)
p value (χ^2 test)	p = 0.0001		p = 0.0001	
Non-responders	179/398 (45%)	101/389 (26%)	200/509 (40%)	105/500 (21%)
Patients with complete response (CR/CRu)	190 (48%)	260 (67%)	268 (53%)	361 (72%)
partial response (PR)	29 (7%)	28 (7%)	41 (8%)	34 (7%)

Efficacy Parameter	Primary Analysis[a]		Updated Analysis[b]	
	Observation N = 513	Rituximab Maintenance N = 505	Observation N = 513	Rituximab Maintenance N = 505
stable disease (SD)	1 (<1%)	0 (0%)	1 (<1%)	1 (<1%)
progressive disease (PD)	162 (41%)	79 (20%)	181 (36%)	86 (17%)
Event-free Survival				
Median time to event (months)	38	NR	48	NR
p value (stratified log-rank test)	p = 0.0001		p = 0.0001	
HR [95% CI] (stratified)	0.54 [0.43;0.69]		0.61 [0.51;0.72]	
Time to Next Anti-Lymphoma Treatment				
Median time to event (months)	NR	NR	71	NR
p value (stratified log-rank test)	p = 0.0003		p < 0.0001	
HR [95% CI] (stratified)	0.61 [0.46;0.80]		0.63 [0.52;0.76]	
Time to Next Chemotherapy Treatment				
Median time to event (months)	NR	NR	85	NR
p value (stratified log-rank test)	p = 0.0011		p = 0.0006	
HR [95% CI] (stratified)	0.60 [0.44;0.82]		0.70 [0.57;0.86]	
Transformation Rate at First Progression				
Patients with progression	173	91	278	186
Patients with transformation	19/513 (4%)	11/505 (2%)	24/513 (5%)	16/505 (3%)

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

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

Maintenance therapy - relapsed/refractory follicular NHL
In a prospective, open label, international, multi-centre, phase III trial, 465 patients with relapsed/refractory follicular NHL were randomised in a first step to induction therapy with either CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone; n=231) or 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 375 mg/m^2 body surface area given every 3 months until disease progression or for a maximum period of two years.

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

Table 6 Induction phase: overview of efficacy results for CHOP vs R-CHOP (31 months median observation time)

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

[1)] Estimates were calculated by hazard ratios

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

Abbreviations: NA, not available; NR, not reached; mo, months; ORR: overall response rate; CR: complete response; PR: partial response; OS: overall survival; PFS: progression free survival

For patients randomised to the maintenance phase of the trial, the median observation time was 28 months from maintenance randomisation. Maintenance treatment with 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% CI; 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% CI; 22% - 75%).

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

Table 8 Maintenance phase: overview of efficacy results 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	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 CR	22.1	51.9	0.0071	46%
PR	14.3	52.8	0.0008	64%
	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) (Table 14). 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). Rituximab maintenance treatment also provided a clinically meaningful benefit in terms of overall survival for both patients responding to CHOP and patients responding to R-CHOP in the induction phase of the study, although longer follow-up is required to confirm this observation.

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

Diffuse large B-cell non-Hodgkin's lymphoma

In a randomised, open-label trial, a total of 399 previously untreated elderly patients (age 60 to 80 years) with diffuse large B-cell lymphoma received standard CHOP chemotherapy (cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2 up to a maximum of 2 mg on day 1, and prednisolone 40 mg/m^2/day on days 1 - 5) every 3 weeks for eight cycles, or 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 randomised patients (197 CHOP, 202 R-CHOP), and had a median follow-up duration of approximately 31 months. The two treatment groups were well balanced in baseline characteristics and disease status. The final analysis confirmed that R-CHOP significantly increased the duration of event-free survival (the primary efficacy parameter, where events were death, relapse or progression of lymphoma, or institution of a new anti-lymphoma treatment) (p=0.0001). Kaplan Meier estimates of the median duration of event-free survival were 35 months in the R-CHOP arm compared to 13 months in the CHOP arm, representing a risk reduction of 41%. At 24 months, estimates for overall survival were 68.2% in the R-CHOP arm compared to 57.4% in the CHOP arm. A subsequent analysis of the duration of overall survival, carried out with a median follow-up duration of 60 months, confirmed the benefit of R-CHOP over CHOP treatment (p=0.0071), representing a risk reduction of 32%.

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

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

Previously untreated and relapsed/refractory chronic lymphocytic leukaemia

In two open-label randomised trials, a total of 817 previously untreated patients and 552 patients with relapsed/refractory CLL were randomised to receive either FC chemotherapy (fludarabine 25 mg/m^2, cyclophosphamide 250 mg/m^2, days 1-3) every 4 weeks for 6 cycles or 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 cycles 2-6. A total of 810 patients (403 R- FC, 407 FC) from the first line study (Table 9 and Table 10) and 552 patients (276 R-FC, 276 FC) for the relapsed/refractory study (Table 11) were analysed for efficacy.

In the first-line study, after a median observation time of 20.7 months, the median progression-free survival (PFS; primary endpoint) was a median of 40 months in the R-FC group and a median of 32 months in the FC group ($p < 0.0001$, log-rank test). The analysis of overall survival demonstrated improved survival in favour of the R-FC arm (p=0.0427, log-rank test). These results were confirmed with longer follow-up: after a median observation time of 48.1 months, the median PFS was 55 months in the R-FC group and 33 months in the FC group ($p < 0.0001$, log-rank test) and overall survival analyses continued to show a significant benefit of R-FC treatment over FC chemotherapy alone ($p = 0.0319$, log-rank test). The benefit in terms of PFS was consistently observed in most patient subgroups analysed according to disease risk at baseline (i.e. Binet stages A-C) and was confirmed with longer follow-up (Table 10).

Table 7 First-line treatment of chronic lymphocytic leukaemia - 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	32.2 (32.8)***	39.8 (55.3)***	< 0.0001 (< 0.0001)***	0.56 (0.55)***
Overall Survival	NR (NR)***	NR (NR)***	0.0427 (0.0319)***	0.64 (0.73)***
Event Free Survival	31.1 31.3***	39.8 (51.8)***	< 0.0001 (< 0.0001)***	0.55 (0.56)***
Response rate (CR, nPR, or PR)	72.7%	86.1%	< 0.0001	n.a.
CR rates	17.2%	36.0%	< 0.0001	n.a.
Duration of response*	34.7 (36.2)***	40.2 (57.3)***	0.0040 (< 0.0001)***	0.61 (0.56)***
Disease free survival (DFS)**	NR (48.9)***	NR (60.3)***	0.7882 (0.0520)***	0.93 (0.69)***
Time to new CLL treatment	NR (47.2)***	NR (69.7)***	0.0052 (< 0.0001)***	0.65 (0.58)***

Response rate and CR rates analysed using Chi-squared Test.
*: only applicable to patients with CR (complete response), nPR (nodular partial response) or PR (partial response) as end of treatment response

**: only applicable to patients with CR as end of treatment response
***: values in brackets correspond to 48.1 months median observation time (ITT population – 409 FC, 408 R-FC)
NR: not reached; n.a. not applicable.

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

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

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

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

Table 8 Treatment of relapsed/refractory chronic lymphocytic leukaemia – 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	20.6	30.6	0.0002	35%
Overall Survival	51.9	NR	0.2874	17%
Event Free Survival	19.3	28.7	0.0002	36%
Response rate (CR, nPR, or PR)	58.0%	69.9%	0.0034	n.a.
CR rates	13.0%	24.3%	0.0007	n.a.
Duration of response*	27.6	39.6	0.0252	31%
Disease free survival (DFS)**	42.2	39.6	0.8842	-6%
Time to new CLL treatment	34.2	NR	0.0024	35%

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

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

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

5.2. Pharmacokinetic Properties

Distribution and elimination

Non-Hodgkin's lymphoma

Based on a population pharmacokinetic analysis in 298 NHL patients who received single or multiple infusions of rituximab as a single agent or in combination with CHOP therapy, the typical population estimates of nonspecific clearance (CL_1), specific clearance (CL_2) likely contributed by B cells or tumour burden, and central compartment volume of distribution (V_1) were 0.14 L/day, 0.59 L/day, and 2.7 L, respectively. The estimated median terminal elimination half-life of rituximab was 22 days (range 6.1 to 52 days). Baseline CD19-positive cell counts and size of measurable tumour lesions contributed to some of the variability in CL_2 of rituximab in data from 161 patients given 375 mg/m^2 as an IV infusion for 4 weekly doses. Patients with higher CD19-positive cell counts or tumour lesions had a higher CL_2. However, a large component of inter-individual variability remained for CL_2 after correction for CD19-positive cell counts and tumour lesion size. V_1 varied by body surface area (BSA) and CHOP therapy. This variability in V (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 mcg/mL (range 77.5 to 996.6 mcg/mL). The peak and trough serum levels of rituximab were inversely correlated with baseline values for the number of circulating CD19-positive B-cells and measures of disease burden. Median steady-state serum levels were higher for responders compared with non-responders. Serum levels were higher in patients with International Working Formulation (IWF) subtypes B, C, and D as compared with those with subtype A. Rituximab was detectable in the serum of patients 3 - 6 months after completion of last treatment.

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

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

Chronic lymphocytic leukaemia

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

Comparability of Truxima® with MabThera®

Truxima® is indicated for treatment of patients with:
Non-Hodgkin's lymphoma

Truxima® is indicated for the treatment of patients with:

- CD20 positive, previously untreated low-grade or follicular, B-cell non-Hodgkin's lymphoma in combination with chemotherapy,

- CD20 positive, relapsed or chemoresistant low-grade or follicular, B-cell non-Hodgkin's lymphoma.

- CD20 positive diffuse large B-cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) chemotherapy.

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

Chronic lymphocytic leukaemia

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

and **is not indicated for use in other conditions**. (see Section 4.1 – THERAPEUTIC INDICATIONS).

This section also summarises information about rituximab in other conditions.

PK equivalence between Truxima (CT-P10) and MabThera® was demonstrated in 1 Phase 3 study (CT-P10 3.3 in AFL patients) in the CT-P10 clinical development program.

Study CT-P10 3.3

Phase 3 study to demonstrate equivalence of pharmacokinetics and non-inferiority of efficacy for CT-P10 in comparison with Rituxan®, each administered in combination with cyclophosphamide, vincristine and prednisone (CVP) in patients with AFL. Study CT-P10 3.3 has been designed to demonstrate PK similarity (Part 1) and therapeutic non-inferiority (Part 2) between CT-P10 and Rituxan® in patients with AFL who received concomitant CVP.

In the PK population, the 90% CIs of ratios of geometric LS means for both AUC_{tau} and $C_{max,ss}$ were entirely contained in the equivalence range of 80% to 125% indicating that rituximab exposures from CT-P10 are similar to those from Rituxan®.

Pharmacokinetics in special populations

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

5.3. Preclinical safety data

Developmental toxicity studies performed in cynomolgus monkeys revealed no evidence of embryotoxicity in utero. New born offspring of maternal animals exposed to rituximab were noted to have depleted B-cell populations during the post natal phase.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Sodium citrate dihydrate

Polysorbate 80

Sodium chloride

Hydrochloric acid or sodium hydroxide (pH adjusted to 6.5).

6.2. Incompatibilities

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

6.3. Shelf life

Truxima® 100 mg

4 years when stored at 2 °C – 8 °C (in a refrigerator)

Truxima® 500 mg

4 years when stored at 2 °C – 8 °C (in a refrigerator)

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

6.4. Special precautions for storage

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

The prepared infusion solution of rituximab is physically and chemically stable for 24 hours at 2 °C - 8 °C and subsequently 12 hours at room temperature (not more than 30 °C).

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

6.5. Nature and contents of container

Truxima® 100 mg in 10 mL glass vial (rituximab 10 mg/mL) 2's.

Truxima® 500 mg in 50 mL glass vial (rituximab 10 mg/mL) 1's.

6.6. Special precautions for disposal and other handling

Withdraw the required amount of Truxima® under aseptic conditions and dilute to a calculated rituximab concentration of 1 – 4 mg/mL in an infusion bag containing sterile, non-pyrogenic 0.9% aqueous saline solution or 5% aqueous dextrose solution. To mix the solution, gently invert the bag to avoid foaming. 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.

Disposal

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

7. MEDICINE SCHEDULE

8. SPONSOR

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