Truxima®

Rituximab

Concentrate for solution for infusion

HEALTHCARE
CELLTRION™

1. PHARMACEUTICAL FORM

Vial 100 mg/10 ml and 500 mg/50 ml.
The content of the vial is a clear to opalescent liquid, colorless to pale yellow.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: rituximab.

3. CLINICAL PARTICULARS

3.1 Therapeutic Indications

Truxima® is indicated for the treatment of patients with relapsed or chemoresistant indolent B-cell non-Hodgkin's lymphomas.
Truxima® is indicated for the treatment of patients with CD20 positive diffuse large B-cell non-Hodgkin's lymphoma (DLCL) in combination with CHOP (cyclophosphamide, doxorubicin vincristine and prednisone) chemotherapy.
Truxima® is indicated for the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with CVP chemotherapy.
Truxima® maintenance therapy is indicated for the treatment of follicular lymphoma patients responding to induction therapy.

Chronic Lymphocytic Leukaemia
Truxima® is indicated in combination with fludarabine and cyclophosphamide (FC), for the treatment of patients with previously untreated and previously treated CD20-positive CLL.

Rheumatoid Arthritis
Truxima® in combination with methotrexate is indicated for the treatment of adult patients with severe active rheumatoid arthritis who have had an inadequate response or intolerance to one or more tumour necrosis factor (TNF) inhibitor therapies.

3.2 Dosage and Method of Administration

3.2.1 Standard Dosage
Truxima® should be administered as an i.v. infusion through a dedicated line, in an environment where full resuscitation facilities are immediately available, and under the close supervision of an experienced physician.
The prepared infusion solution must not be administered as an i.v. injection or bolus infusion.
Premedication consisting of an analgesic/antipyretic (e.g. paracetamol) and an antihistaminic drug (e.g. diphenhydramine) should always be administered before each infusion of Truxima®. Premedication with corticosteroids should also be considered.
Patients should be closely monitored for the onset of cytokine release syndrome (see section 3.4). Patients who develop evidence of severe reactions, especially severe dyspnea, bronchospasm and hypoxia should have the infusion interrupted immediately. The patient should then be evaluated for evidence of tumour lysis syndrome including appropriate laboratory tests and, for pulmonary infiltration, with a chest x-ray. The infusion should not be restarted until complete resolution of all symptoms, and normalisation of laboratory values and chest x-ray findings. At this time, the infusion can be initially resumed at not more than one-half the previous rate. If the same severe adverse reactions occur for a second time the decision to stop the treatment should be seriously considered on a case by case basis.
Mild or moderate infusion-related reactions (see section 3.8) usually respond to a reduction in the rate of infusion. The infusion rate may be increased upon improvement of symptoms.

Low-grade or follicular non-Hodgkin's lymphoma
Initial treatment
The recommended dosage of Truxima® used as monotherapy for adult patients is 375 mg/m^2 body surface area, administered as an i.v. infusion once weekly for 4 weeks.
The recommended dosage of Truxima® in combination with CVP chemotherapy is 375 mg/m^2 body surface area for 8 cycles (21 days/cycle), administered on day 1 of each chemotherapy cycle after IV administration of the corticosteroid component of CVP. Rituximab has shown acceptable safety in combination with other chemotherapies e.g. CHOP.

Re-treatment following relapse
Patients who have responded to rituximab initially have been treated again with rituximab at a dose of 375 mg/m^2 body surface area, administered as an i.v. infusion once weekly for 4 weeks (see *Re-treatment, weekly for 4 doses*).

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

Relapsed/refractory follicular lymphoma
Patients who have responded 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.

Diffuse large B-cell non-Hodgkin's lymphoma
Truxima® should be used in combination with CHOP chemotherapy. The recommended dosage of Truxima® is 375 mg/m^2 body surface area, administered on day 1 of each chemotherapy cycle after i.v. administration of the corticosteroid component of CHOP. The other components of CHOP (cyclophosphamide, doxorubicin and vincristine) should be given after the administration of Truxima®. Safety and efficacy of rituximab have not been established in combination with other chemotherapies.

Chronic Lymphocytic Leukaemia
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 x10^9/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.
The dose for CLL is 375 mg/m^2 in the first cycle and 500 mg/m^2 in cycles 2–6, in combination with FC, administered every 28 days.

First infusion
The recommended initial infusion rate is 50 mg/h; subsequently, the rate can be escalated in 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 CVP chemotherapy, standard dose reductions for the chemotherapeutic medicinal products should be applied.

Rheumatoid arthritis
A course of Truxima® consists of two 1000 mg i.v. infusions. The recommended dosage of Truxima® is 1000 mg by i.v. infusion followed two weeks later by the second 1000 mg i.v. infusion.
Patients may receive further courses of treatment, based on signs and symptoms of disease. In clinical studies, no patient received a second course of rituximab treatment within 16 weeks of the first infusion of the first course. The time interval between courses was variable, with the majority of patients receiving further therapy 6-12 months after the previous course. Some patients required even less frequent retreatment. The efficacy and safety of further courses is comparable to the first course. (See sections 3.8.2 and 4.1.2.3).
Rheumatoid arthritis patients should receive treatment with 100 mg i.v. methylprednisolone 30 minutes prior to Truxima® to decrease the rate and severity of acute infusion reactions (see section 3.4).
Dosage adjustments during treatment:
First infusion of each course:
The recommended initial rate for infusion is 50 mg/hr; after the first 30 minutes, it can be escalated in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.
Second infusion of each course:
Subsequent doses of Truxima® IV can be infused at an initial rate of 100 mg/hr, and increased by 100 mg/hr increments at 30 minutes intervals, to a maximum of 400 mg/hr.

Rheumatoid Arthritis Only;
Alternative subsequent, faster, infusions schedule:
In RA, with a dose of 1000 mg Truxima®, if there are no infusion related reactions or other reasons to slow or cease the infusion, the standard infusion schedules shown above result in an estimated duration of infusion of 4h 15 minutes for the first infusion and 3h 15 minutes for the second infusion in each course.
If patients did not experience a serious infusion-related adverse event with their first or subsequent infusions of a dose of 1000 mg Truxima® administered over the standard infusion schedule, a more rapid infusion can be administered for second and subsequent infusions using the same concentration as in previous infusions (4 mg/ml in a 250 ml volume). Initiate at a rate of 250mg/hour for the first 30 minutes and then 600 mg/hour for the next 90 minutes. If the more rapid infusion is tolerated, this infusion schedule can be used when administering subsequent infusions. With this infusion schedule, the 1000 mg/250 ml infusion will generally be completed in 2 h.
Patients who have clinically significant cardiovascular disease including arrhythmias or previous serious infusion reactions to any prior biologic therapy or to rituximab, should not be administered the more rapid infusion.

Special Dosage Instructions
Pediatric use:
The safety and effectiveness of rituximab in pediatric patients (<18 years) have not been established. Hypogammaglobulinaemia has been observed in pediatric patients treated with rituximab, in some cases severe and requiring long-term immunoglobulin substitution therapy. The consequences of long term B cell depletion in pediatric patients are unknown.

3.3 Contraindications

Truxima® is contraindicated in patients with known hypersensitivity to rituximab, to any of its excipients or to murine proteins.
Active, severe infections.

3.4 Special Warnings and Special Precautions for Use

Special warnings and precautions for use – for all patients
In order to improve the traceability of biological medicinal products, the trade name of the administered product should be clearly recorded (or stated) in the patient file.

Interchangeability and substitutability
Truxima® is not interchangeable or substitutable with other preparation of rituximab products.

Progressive multifocal leukoencephalopathy
Use of Truxima® may be associated with an increased risk of Progressive Multifocal Leukoencephalopathy (PML). Patients must be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML. If PML is suspected, further dosing must be suspended until PML has been excluded. The clinician should evaluate the patient to determine if the symptoms are indicative of neurological dysfunction, and if so, whether these symptoms are possibly suggestive of PML. Consultation with a Neurologist should be considered as clinically indicated.
If any doubt exists, further evaluation, including MRI scan preferably with contrast, CSF testing for JC Viral DNA and repeat neurological assessments, should be considered.
The physician should be particularly alert to symptoms suggestive of PML that the patient may not notice (e.g. cognitive, neurological or psychiatric symptoms). Patients should also be advised to inform their partner or caregivers about their treatment, since they may notice symptoms that the patient is not aware of.
If a patient develops PML the dosing of Truxima® must be permanently discontinued.
Following reconstitution of the immune system in immunocompromised patients with PML, stabilisation or improved outcome has been seen. It remains unknown if early detection of PML and suspension of rituximab therapy may lead to similar stabilisation or improved outcome.

3.4.1 Non-Hodgkin's Lymphoma Patients and Chronic Lymphocytic Leukaemia Patients
Infusion/administration-related reactions: rituximab is associated with infusion/administration-related reactions, which may be related to release of cytokines and/or other chemical mediators. Cytokine release syndrome may be clinically indistinguishable from acute hypersensitivity reaction.

• Infusion-related reactions for rituximab IV
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 sections 3.4 and 3.8). 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 and when other therapeutic alternatives have been exhausted. 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 Truxima®.

Pulmonary events: Pulmonary events have included hypoxia, pulmonary infiltrates, 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 3.2) 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. 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 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.
Truxima® infusions should be administered in an environment where full resuscitation facilities are immediately available, and under the close supervision of an experienced oncologist/ hematologist.

Cardiovascular: Since hypotension may occur during rituximab administration, consideration should be given to withholding antihypertensive medications 12 hours prior to and throughout Truxima® administration. Angina pectoris or cardiac arrhythmia, such as atrial flutter and fibrillation, heart failure and/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 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 Truxima®. When Truxima® is given in combination with CHOP or CVP chemotherapy, regular full blood counts should be performed according to usual medical practice.

Infections: Serious infections, including fatalities, can occur during therapy with rituximab. Truxima® should not be administered to patients with an active, severe infection.
Physicians should exercise caution when considering the use of Truxima® in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection.

Hepatitis B Infections: Cases of hepatitis B reactivation, some of which were fatal, including reports of fulminant hepatitis, 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 Truxima®. At minimum this should include HBsAg-status and HBcAb-status. These can be complemented with other appropriate markers as per local guidelines. Patients with active hepatitis B disease should not be treated with Truxima®. Reactivation of HBV infection is a well-known complication in patients with chronic hepatitis B, especially in those receiving cytotoxic or immunosuppressive therapy. In addition, hematological malignancies may be a risk factor for HBV reactivation. 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.
The following additional serious viral infections, either new, reactivated or exacerbated, have been identified in clinical studies or post-marketing reports. The majority of patients were profoundly immune-suppressed. These viral infections included JC virus [progressive multifocal leucoencephalopathy (PML)], cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus and hepatitis C. In some cases, the viral infections occurred up to one year following discontinuation of rituximab and have resulted in death.
Very rare cases of progressive multifocal leukoencephalopathy (PML) have been reported during postmarketing use of rituximab in NHL and CLL (see section 3.8). The majority of patients had received rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant.

Skin reactions: Severe skin reactions such as Toxic Epidermal Necrolysis and Stevens-Johnson Syndrome, some with fatal outcome, have been reported (see section 3.8). In case of such an event with a suspected relationship to Truxima®, 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 Truxima® may receive non-live vaccinations. However, with non-live vaccines response rates may be reduced. In a nonrandomized 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.

3.4.2 Rheumatoid Arthritis Patients
Special warnings and precautions for use – for patients with rheumatoid arthritis
Methotrexate (MTX) naïve populations
The use of Truxima® is not recommended in MTX-naïve patients since a favourable benefit risk relationship has not been established.

Concomitant/sequential use of other DMARDs
The concomitant use of Truxima® and antirheumatic therapies other than those specified under the rheumatoid arthritis indication and posology is not recommended.
There are limited data from clinical trials to fully assess the safety of the sequential use of other DMARDs (including TNF inhibitors and other biologics) following rituximab. The available data indicate that the rate of clinically relevant infection is unchanged when such therapies are used in patients previously treated with rituximab, however patients should be closely observed for signs of infection if biologic agents and/or DMARDs are used following Truxima® therapy.

Malignancy
Immunomodulatory drugs may increase the risk of malignancy. On the basis of limited experience with rituximab in rheumatoid arthritis patients a possible risk for the development of solid tumours cannot be excluded at this time, although present data do not seem to suggest any increased risk.

Infusion-related Reactions
Truxima® is associated with infusion-related reactions, which may be related to release of cytokines and/or other chemical mediators. Premedication with IV glucocorticoid significantly reduced the incidence and severity of these events and should be administered prior to Truxima® treatment (See section 3.2 and section 3.8).

Most infusion events reported were mild to moderate in severity. The most common symptoms were headache, pruritus, throat irritation, flushing, rash, urticaria, hypertension, and pyrexia. In general, the proportion of patients experiencing any infusion reaction was higher following the first infusion of any treatment course than following the second infusion.
Subsequent rituximab infusions were better tolerated by patients than the initial infusion. Fewer than 1% of patients experienced serious IRRs, with most of these reported during the first infusion of the first course (see section 3.8). The reactions reported were usually reversible with a reduction in rate, or interruption, of rituximab infusion and administration of an anti-pyretic, an antihistamine, and, occasionally, oxygen, IV saline or bronchodilators, and glucocorticoids if required. 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.

Hypersensitivity Reactions / Anaphylaxis
Anaphylactic and other hypersensitivity reactions have been reported following the intraveneous 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 Truxima®.

Cardiovascular
Since hypotension may occur during Truxima® infusion, consideration should be given to withholding anti-hypertensive medications 12 hours prior to the Truxima® infusion.
Angina pectoris, or cardiac arrhythmias such as atrial flutter and fibrillation heart failure or myocardial infarction have occurred in patients with non-Hodgkin's lymphoma treated with rituximab. Therefore patients with a history of cardiac disease and/or those receiving cardiotoxic drug therapy should be monitored closely during infusions.

Infections
Based on the mechanism of action of Truxima® and the knowledge that B cells play an important role in maintaining normal immune response, patients may have an increased risk of infection following Truxima® therapy. Truxima® 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 Truxima® in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection (see section 3.8). Patients who develop infection following Truxima® therapy should be promptly evaluated and treated appropriately.
In patients with non-Hodgkin's Lymphoma receiving rituximab in combination with cytotoxic chemotherapy, very rare cases of hepatitis B reactivation have been reported (see 3.4.1).

Hepatitis B Infections
Cases of hepatitis B reactivation including those with a fatal outcome, have been reported in RA patients receiving rituximab.
Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with Truxima®. At minimum this should include HBsAg-status and HBcAb-status. These can be complemented with other appropriate markers as per local guidelines. Patients with active hepatitis B disease should not be treated with Truxima®. 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 3.8). In case of such an event with a suspected relationship to Truxima®, 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 (including RA). Several, but not all of the reported cases had potential multiple 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. The efficacy and safety of rituximab for the treatment of autoimmune diseases other than rheumatoid arthritis has not been established.

Immunization
Physicians should review the patient's vaccination status and follow current immunization guidelines prior to Truxima® therapy and follow local/national guidance for adult vaccination against infectious disease. Vaccination should be completed at least 4 weeks prior to first administration of Truxima®.
The safety of immunization with live viral vaccines following Truxima® therapy has not been studied. Therefore vaccination with live virus vaccines is not recommended whilst on Truxima® or whilst peripherally B cell depleted.
Patients treated with Truxima® may receive non-live vaccinations. However, response rates to non-live vaccines may be reduced. In a randomized study, patients with RA treated with rituximab and methotrexate had comparable response rates to tetanus recall antigen (39% vs 42%), reduced rates to pneumococcal polysaccharide vaccine (43% vs 82% to at least 2 pneumococcal antibody serotypes), and KLH neoantigen (34% vs 80%), when given at least 6 months after rituximab as compared to patients only receiving methotrexate. Should non-live vaccinations be required whilst receiving Truxima® therapy, these should be completed at least 4 weeks prior to commencing the next course of Truxima®.
In the overall experience of rituximab repeat treatment over one year, the proportions of patients with positive antibody titers against S. pneumoniae, influenza, mumps, rubella, varicella and tetanus toxoid were generally similar to the proportions at baseline.

3.5 Interactions with other Medical Products and other Forms of Interaction

At present, there are limited data available 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.

3.6 Pregnancy and Lactation

Females and Males of Reproductive Potential
• ***Fertility***

No preclinical fertility studies have been conducted
• ***Animal 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.

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

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 Truxima® should not be administered to pregnant women unless the possible benefit outweighs the potential risk.

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

3.7 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.

3.8 Undesirable Effects

3.8.1 Experience from non-Hodgkin's lymphoma and chronic lymphocytic leukaemia
The overall safety profile of rituximab in non-Hodgkin's lymphoma and chronic lymphocytic leukaemia is based on data from patients from clinical trials and from post-marketing surveillance.
These patients were treated either with rituximab monotherapy (as induction treatment or maintenance treatment following induction treatment) or in combination with chemotherapy.
The most frequently observed adverse drug reactions (ADRs) in patients receiving rituximab were infusion-related reactions 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 trial in patients with CLL.
The most frequent reported or observed serious adverse drug reactions were:
• Infusion-related reactions (including cytokine-release syndrome, tumour-lysis syndrome), see section 3.4.
• Infections, see section 3.4.
• Cardiovascular events, see section 3.4.
Other serious ADRs reported include hepatitis B reactivation and PML (see section 3.4.).
The frequencies of ADRs reported with rituximab alone or in combination with chemotherapy are summarised in the tables below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as very common (≥1/10), common (≥1/100 to < 1/10) and uncommon (≥1/1,000 to < 1/100) and rare (≥1/10,000 to < 1/1000). The ADRs identified only during post-marketing surveillance, and for which a frequency could not be estimated, are listed under "unknown".

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

System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not known[8]
Infections and infestations	Bacterial infections, viral infections, [+] bronchitis	Sepsis, [+] pneumonia, [+] febrile infection, [+] herpes zoster, [+] respiratory tract infection, fungal infections, infections of unknown aetiology, [+] acute bronchitis, [+] sinusitis, hepatitis B[1]		Serious viral infection[2]		
Blood and the lymphatic system disorders	Neutropenia, leucopenia, [+] febrile Neutropenia, [+] thrombocytopenia	Anaemia, pancytopenia, [+] granulocytopenia	Coagulation disorders, aplastic anaemia, haemolytic anaemia, lymphadenopathy		Transient increase in serum IgM levels[3]	Late neutropenia[3]

System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not known[8]
Immune system disorders	Infusion related Reactions[4], angioedema	Hypersensitivity		Anaphylaxis	Tumour lysis syndrome, cytokine release syndrome[4], serum sickness	infusion-related acute reversible thrombocytopenia[4]
Metabolism and nutrition disorders		Hyperglycaemia, weight decrease, peripheral 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[4 and 6], arrhythmia, +atrial fibrillation, tachycardia, +cardiac disorder	+Left ventricular failure, +supraventricular tachycardia, +ventricular tachycardia, +angina, +myocardial ischaemia, bradycardia	severe cardiac events[4 & 6]	Heart failure[4 & 6]	
Vascular disorders		Hypertension, orthostatic hypotension, hypotension			Vasculitis (predominately cutaneous), leukocyte-clastic vasculitis	
Respiratory, thoracic and mediastinal disorders		Bronchospasm[4], respiratory disease, chest pain, dyspnoea, increased cough, rhinitis	Asthma, bronchiolitis obliterans, lung disorder, hypoxia	Interstitial lung disease[7]	Respiratory failure[4]	lung infiltration
Gastrointestinal disorders	Nausea	Vomiting, diarrhea, abdominal pain, dysphagia, stomatitis, constipation dyspepsia, anorexia, throat irritation	Abdominal enlargement		Gastrointestinal perforation[7]	
Skin and subcutaneous tissue disorders	Pruritis, rash, +alopecia	Urticaria, sweating, night sweats, +skin disorder			Severe bullous skin reactions, toxic epidermal necrolysis[7], Stevens-Johnson syndrome	
Musculoskeletal, connective tissue and bone disorders		Hypertonia, myalgia, arthralgia, back pain, neck pain, pain				
Renal and urinary disorders					Renal failure[4]	
General disorders and administration site conditions	Fever, chills, asthenia, headache	Tumour pain, flushing, malaise, cold syndrome, +fatigue, +shivering, +multi-organ failure[4]	infusion site pain			
Investigations	Decreased IgG levels					

For each term, the frequency count was based on reactions 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 the trials is reported.

[1] includes reactivation and primary infections; frequency based on R-FC regimen in relapsed/refractory CLL
[2] see also section infection below
[3] see also section haematologic adverse reactions below
[4] see also section infusion-related reactions below. Rarely fatal cases reported
[5] signs and symptoms of cranial neuropathy. Occurred at various times up to several months after completion of rituximab 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
[8] Frequency not known (cannot be estimated from the available data)

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

Administration-related reactions

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 one to two hours. These symptoms mainly comprised fever, chills and rigors. Other symptoms included flushing, angioedema, bronchospasm, vomiting, nausea, urticaria/rash, fatigue, headache, throat irritation, rhinitis, pruritus, pain, tachycardia, hypertension, hypotension, dyspnoea, dyspepsia, asthenia and features of tumor 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 and pulmonary oedema and acute reversible thrombocytopenia. Exacerbations of pre-existing cardiac conditions such as angina pectoris or congestive heart failure or severe cardiac events (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.

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.

Localized candida infections as well as Herpes zoster was reported at a higher incidence in the rituximab-containing arm of randomized 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 hematopoetic 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 hepatitis B reactivation, have been reported, the majority of which were in subjects 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.

Maintenance Treatment (NHL) up to 2 years

Data from a phase III clinical trial included 2 cases of fatal PML in NHL patients that occurred after disease progression and retreatment (see section 3.4).

Hematologic events

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. 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 and the neutropenia was not prolonged in the rituximab group plus chemotherapy group. 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 events

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 ischemia) 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

Respiratory failure/insufficiency and pulmonary infiltrates in the context of infusion-related reactions (see section 3.4). In addition to pulmonary events associated with infiltrates outside of infusions,-related reactions and interstitial lung disease, pneumonitis have some with fatal outcome, has been reported rarely.

Neurologic events

During the treatment period, 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 % RFC, 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 recognized risk factors for PRES/RPLS, including the patients' underlying disease, hypertension, immunosuppressive therapy and/or chemotherapy.

Gastrointestinal Disorders

Gastrointestinal perforation in some cases leading to death has been observed in patients receiving 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, 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 observation 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).

Patient subpopulations -rituximab monotherapy

Elderly patients (≥ 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 patients (≥ 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.

3.8.2 Experience from Rheumatoid Arthritis

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

The safety profile of rituximab in patients with severe rheumatoid arthritis (RA) is summarized in the sections below. In clinical trials more than 3100 patients received at least one treatment course and were followed for periods ranging from 6 months to over 5 years; approximately 2400 patients received two or more courses of treatment with over 1000 having received 5 or more courses. The safety information collected during post marketing experience reflects the expected adverse reaction profile as seen in clinical trials for rituximab (see section 3.4)

Patients received 2 x 1000 mg of rituximab separated by an interval of two weeks; in addition to methotrexate (10-25 mg/week). Rituximab infusions were administered after an intravenous infusion of 100 mg methylprednisolone; patients also received treatment with oral prednisone for 15 days. Events are listed in Table 2.Frequencies are defined as very common (≥1/10) and common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), and very rare (<1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The most frequent adverse reactions considered due to receipt of rituximab were infusion related reactions. The overall incidence of IRRs in clinical trials was 23% with the first infusion and decreased with subsequent infusions. Serious IRRs were uncommon (0.5% of patients) and were predominantly seen during the initial course. In addition to adverse reactions seen in RA clinical trials for rituximab, progressive multifocal leukoencephalopathy (PML) (see section 3.4) and serum sickness-like reaction have been reported during post marketing experience.

Table 2 Summary of Adverse Drug Reactions Reported in Clinical Trials or During Postmarketing Surveillance Occurring in Patients with Rheumatoid Arthritis receiving rituximab

System Organ Class	Very Common	Common	Uncommon	Rare	Very rare
Infections and Infestations	Upper respiratory tract infection, urinary tract infection	Bronchitis, sinusitis, gastroenteritis, tinea pedis			PML, reactivation of hepatitis B
Blood and lymphatic system disorders		neutropenia[1]		late neutropenia[2]	Serum sickness-like reaction
Cardiac Disorders				Angina pectoris, atrial fibrillation, heart failure, myocardial infarction	Atrial flutter
Immune System Disorders / **General disorders and administration site conditions**	* Infusion related reactions (hypertension, nausea, rash, pyrexia, pruritus, urticaria, throat irritation, hot flush, hypotension rhinitis, rigors, tachycardia, fatigue, oropharyngeal pain, peripheral oedema, erythema			* Infusion related reactions (generalized oedema, bronchospasm wheezing, laryngeal oedema, angioneurotic oedema, generalized pruritis, anaphylaxis, anaphylactoid reaction	
Metabolism and Nutritional Disorders		Hypercholesterolemia			
Nervous System disorders	Headache	Paraesthesia, migraine, dizziness, sciatica			
Skin and subcutaneous tissue disorders		Alopecia			Severe bullous skin reactions, toxic epidermal necrolysis[5], Stevens-Johnson syndrome
Psychiatric disorders		Depression, anxiety			
Gastrointestinal Disorders		Dyspepsia, diarrhoea, gastro-oesophageal reflux, mouth ulceration, upper abdominal pain			
Musculoskeletal disorders		Arthralgia/ musculoskeletal pain, osteoarthritis, bursitis			
Investigations	decreased IgM levels[4]	decreased IgG levels[4]			

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

Multiple Courses

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

Infusion-related reactions

The most frequent ADRs following receipt of rituximab in clinical studies were infusion-related reactions (IRRs) (refer to Table 2). Among the 3189 patients treated with tituximab, 1135 (36%) experienced at least one IRR with 733/3189 (23%) of patients experiencing an IRR following first infusion of the first exposure to rituximab. The incidence of IRRs decline for all subsequent infusions.

In clinical studies fewer than 1% (17/3189) of patients experienced a serious IRR. There were no CTC Grade 4 IRRs and no deaths due to IRRs. The proportion of CTC Grade 3 events, and of IRRs leading to withdrawal decreased by course and were rare from course 3 onwards.

Signs and or symptoms suggesting an infusion-related reaction (e.g. nausea, pruritis, fever, urticaria/rash, chills, pyrexia, rigors, sneezing, angioneurotic edema, throat irritation, cough and bronchospasm, with or without associated hypotension or hypertension) were observed in 720/3095 (23%) patients following first infusion of the first exposure to rituximab; Premedication with intravenous glucocorticoid significantly reduced the incidence and severity of these events. (see section 3.4).

In a study designed to evaluate the safety of a 120-minute rituximab infusion in patients with rheumatoid arthritis, patients with moderate-to-severe active RA who did not experience a serious infusion-related reaction (IRR) during or within 24 hours of their first studied infusion were allowed to receive a 120-minute infusion of rituximab. Patients with a history of a serious infusion reaction to a biologic therapy for RA were excluded from entry. The incidence, types and severity of infusion-related reactions (IRRs) were consistent with that observed historically. No serious IRRs were observed (see section 4.1.2 Clinical/Efficacy Studies).

Infections

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

Cases of Progressive Multifocal Leukoencephalopathy with fatal outcome have been reported following use of rituximab for the treatment of autoimmune diseases. This includes Rheumatoid Arthritis and off-label autoimmune diseases, including Systemic Lupus Erythematosus (SLE) and Vasculitis. All the reported cases had multiple risk factors for PML, including either the underlying disease and or long-term immunosuppressive therapy or chemotherapy.

Malignancies

In RA clinical studies, the incidence of malignancy following exposure to rituximab is 0.8 per 100 patient years, which is within the range expected for an age- and gender- matched population.

Cardiovascular

Cardiac events were observed in 11 % patients in clinical studies with rituximab. In placebo controlled studies, serious cardiac events were reported equally in rituximab and placebo treated patients (2 %).

Neurologic events

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.

3.9 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 re B cell-depleted.

4. PHARMACOLOGICAL PROPERTIES & EFFECTS

4.1 Pharmacodynamic Properties

4.1.1 Mechanism of Action

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

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

Peripheral B-cell counts declined to levels below normal following the first dose of rituximab. In patients treated for hematological malignancies, B cell repletion began within 6 months of treatment returning to normal levels between 9 and 12 months after completion of therapy. The majority of patients received further treatment prior to full B cell repletion. A small proportion of patients had prolonged peripheral B cell depletion lasting 2 years of more after their last dose of rituximab.

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.

4.1.2 Efficacy / Clinical Studies

4.1.2.1 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 i.v. 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-center, single-arm study, 37 patients with relapsed or chemoresistant, low grade or follicular B–cell NHL received 375 mg/m^2 of rituximab as i.v. 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 i.v. 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-center, single-arm study, 58 patients with relapsed or chemoresistant low grade or follicular B–cell NHL, who had achieved an objective clinical response to a prior course of rituximab, were re-treated with 375 mg/m^2 of rituximab as i.v. 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% (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 favorably with the TTP achieved after the prior course of rituximab (12.4 months).

In combination with CVP chemotherapy

Initial treatment

In an open-label randomized trial, a total of 322 previously untreated low-grade or follicular B-cell NHL patients 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. At the time of the final analysis, the median observation time was 18 months. R-CVP led to a significant benefit over CVP for the primary endpoint, time to treatment failure (25.9 months vs. 6.7 months, p < 0.0001, log-rank test). The risk of experiencing a treatment failure event was reduced by 67% (95% CI: 56% - 76%) with R-CVP compared with CVP alone, using a Cox regression analysis. The Kaplan-Meier estimated event-free rate at 12 months was 69% in the R-CVP group compared with 32% in the CVP group. 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%). At 18 months, the median duration of response had not been reached in the R-CVP group and was 9.8 months in the CVP group (p < 0.0001, log-rank test). Amongst responding patients, Cox regression analysis showed that the risk of relapse was reduced by 70% (95% CI: 55% - 81%) in the R-CVP group compared to the CVP group.

The time to institution of new lymphoma treatment or death was significantly longer in the R-CVP group (not estimable), compared to the CVP group (12.3 months) (p < 0.0001, log-rank test). Treatment with R-CVP significantly prolonged the time to disease progression or death compared to CVP, 27 months and 14.5 months, respectively. At 12 months, 81% in the R-CVP group had not relapsed compared to 58% of patients receiving CVP.

A subsequent analysis of the primary and all secondary parameters, carried out with a median observation time of approximately 42 months, confirmed the benefit of R-CVP over CVP (Table 3).

Table 3 Overview of updated efficacy results of CVP vs R-CVP (42 months median observation time)

	Kaplan-Meier Estimate of Median Time to Event (months)[§]			Treatment Effect[+]
	CVP	R-CVP	Log-Rank p value	
Median Observation Time (months)	41.3	42.1		
Primary Efficacy Parameter				
TTF	6.6	27.0	< 0.0001	66%
Secondary Efficacy Parameters				
Time to disease progression or death[x]	14.5	33.6	< 0.0001	58%
Overall Survival	NR	NR	0.0700	38%
Overall Tumour Response (CR, CRu, PR)*	57%	81%	< 0.0001**	3.2***
Duration of Response	13.5	37.7	< 0.0001	65%
Disease-Free Survival Time to new lymphoma treatment or death	20.5 12.3	44.8 46.3	0.0005 < 0.0001	71% 63%

[§] According to investigator's assessment, all data stratified by center
[+] Treatment effect: for event-free parameters, estimates were calculated by risk reduction; for tumour response, odds ratio was used. NR: not reached since the Kaplan-Meier estimates of event-free rates were above 50% during the entire observation period of the study
[x] Defined as a secondary efficacy parameter in amendment G of the protocol
* Overall response rate is calculated from the tumour response as assessed at the end of trial treatment
** chi-square test;
*** odds ratio
Abbreviations: NR, not reached; TTF: time to treatment failure; CR: complete response; CRu: complete response unconfirmed; PR: partial response.

The rate of cause-specific deaths (death due to lymphoma) was significantly lower in the R-CVP arm when compared to the CVP arm (p=0.02 with stratification by center, log-rank test; 3-year event free rate 93% for R-CVP versus 85% for CVP).

The benefit of adding rituximab to CVP was seen consistently throughout the population recruited in study M39021; [randomized according to BNLI criteria (no versus yes), age (≤ 60 years, > 60 years), number of extra-nodal sites (0-1 versus >1), bone marrow involvement (no versus yes), LDH (elevated, not elevated), β2-microglobulin (elevated, not elevated), B symptoms (absent, present), bulky disease (absent, present), number of nodal sites (< 5 versus ≥ 5), hemoglobin (≤ 12 g/dL versus >12 g/dL), IPI (≤ 1 versus > 1), and FLIPI index (0-2 versus 3-5)].

Maintenance therapy

Previously untreated follicular lymphoma

In a prospective, open label, international, multi-center, phase III trial 1193 patients with previously untreated advanced follicular lymphoma received induction therapy with R-CHOP (n=881), R-CVP (n=268) or R-FCM (n=44), according to the investigators' choice. A total of 1078 patients responded to induction therapy, of which 1018 were randomized 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 2 months until disease progression or for a maximum period of two years.

After a median observation time of 25 months from randomization, maintenance therapy with 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 (Table 4).
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 4).
The updated analysis corresponding to a median observation time of 73 months from randomization confirm the results of the primary analysis (Table 4).

Table 4 Overview of efficacy results for maintenance rituximab vs. observation (25 and 73 months median observation time)

	Observation N = 513	Rituximab N = 505	Log-rank P value	Risk reduction
Primary Efficacy				
PFS (median)	48.5 months *[48.4 months]* (NR)	NR *[NR]* (NR)	<0.0001 *[<0.0001]* (<0.0001)	42% *[45%]* (50%)
Secondary Efficacy				
EFS (median)	48.4 months *[47.6 months]* (37.8 months)	NR *[NR]* (NR)	<0.0001 *[<0.0001]* (<0.0001)	39% *[42%]* (46%)
OS (median)	NR *[NR]* (NR)	NR *[NR]* (NR)	0.8959 *[0.9298]* (0.7246)	-2% *[-2%]* (11%)
TNLT (median)	71.0 months *[60.2 months]* (NR)	NR *[NR]* (NR)	<0.0001 *[<0.0001]* (0.0003)	37% *[39%]* (39%)
TNCT (median)	85.1 months *[NR]* (NR)	NR *[NR]* (NR)	0.0006 *[0.0006]* (0.0011)	30% *[34%]* (40%)
ORR*	60.7% *[60.7%]* (55.0%)	79.0% *[79.0%]* (74.0%)	<0.0001# *[<0.0001#]* (< 0.0001)	OR=2.43 *[OR=2.43]* (OR =2.33)
Complete Response (CR/CRu) rate*	52.7% *[52.7%]* (47.7%)	66.8% *[72.2%]* (66.8%)	<0.0001 *[<0.0001]* (< 0.0001)	OR=2.34 *[OR=2.34]* (OR = 2.21)

* At end of maintenance/observation; # p values from chi-squared test
Main values correspond to 73 months median observation time, italicized values in brackets correspond to 48 months median observation time, and values in parentheses correspond to 25 months median observation time (primary analysis). PFS: progression-free survival; EFS: event-free survival; OS: overall survival; TNLT: time to next anti-lymphoma treatment; TNCT: time to next chemotherapy treatment; ORR: overall response rate; NR: not reached at time of clinical cut-off, OR: odds ratio.

Rituximab maintenance treatment provided consistent benefit in all predefined subgroups tested: gender (male, female), age (<60 years, >= 60 years), FLIPI score (<=1, 2 or >= 3), induction therapy (R-CHOP, R-CVP or R-FCM) and regardless of the quality of response to induction treatment (CR/CRu 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.
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/m² 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).

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				
ORR2)	74%	87%	0.0003	na
CR2)	16%	29%	0.0005	na
PR2)	58%	58%	0.9449	na
Secondary Efficacy				
OS (median)	NR	NR	0.0508	32%
PFS(median)	19.4 mo.	33.2 mo.	0.0001	38%

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

For patients randomized to the maintenance phase of the trial, the median observation time was 28 months from maintenance 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 6). The risk of relapse in complete responders was reduced by 67% (95% CI; 39%-82%).

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) (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.
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 versus >0), B symptoms (absent, present), bone marrow involvement (no versus yes), IPI (0-2 versus 3-5), FLIPI score (0-1, versus 2 versus 3-5), number of extra-nodal sites (0-1 versus >1), number of nodal sites (< 5 versus ≥ 5), number of previous regimens (1 versus 2), best response to prior therapy (CR/PR versus NC/PD), hemoglobin (< 12 g/dL versus ≥ 12 g/dL), β 2-microglobulin (< 3mg/L versus ≥ 3 mg/L), LDH (elevated, not elevated) except for the small subgroup of patients with bulky disease.

4.1.2.2 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/m², doxorubicin 50 mg/m², vincristine 1.4 mg/m² up to a maximum of 2 mg on day 1, and prednisone 40 mg/m²/day on days 1 - 5) every 3 weeks for eight cycles, or rituximab 375 mg/m² 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 38 months, confirmed the benefit of R-CHOP over CHOP treatment (p=0.0094), representing a risk reduction of 33%.
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, β2 microglobulin, LDH, albumin, B symptoms, bulky disease, extranodal sites, bone marrow involvement), the risk ratios for event-free survival and overall survival (R-CHOP compared with CHOP) were less than 0.83 and 0.95, respectively. R-CHOP was associated with improvements in outcome for both high- and low-risk patients according to age-adjusted IPI.

4.1.2.3 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 25mg/m², cyclophosphamide 250 mg/m², 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/m² during the first cycle one day prior to chemotherapy and at a dosage of 500 mg/m² on day 1 of each subsequent treatment cycle. Patients were excluded from the study in relapsed/refractory CLL if they had previously been treated with monoclonal antibodies or if they were refractory (defined as failure to achieve a partial remission for at least 6 months) to fludarabine or any nucleoside analogue. A total of 810 patients (403 R-FC, 407 FC) the first line study (Table 7a and 7b) and 552 patients (276 R-FC, 276 FC) for the relapsed/refractory study Table 8 were analyzed for efficacy.
In the first line study, the median progression-free survival (primary endpoint) was 40 months in the R-FC group and 32 months in the FC group (p < 0.0001, log-rank test). The analysis of overall survival showed an improved survival in favour of the R-FC arm (p=0.0427, log-rank test), however longer follow-up is needed to confirm this observation. The benefit in terms of PFS was consistently observed in most patient subgroups analyzed according to disease risk at baseline.

Table 7a 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)			Risk Reduction
	FC (N = 407)	R-FC (N=403)	Log-Rank p value	
Progression-free survival (PFS)	*32.2*	*39.8*	*<0.0001*	*44%*
Overall Survival	*NR*	*NR*	*0.0427*	*36%*
Event Free Survival	*31.1*	*39.8*	*<0.0001*	*45%*
Response rate (CR, nPR,or PR) *CR rates* *Duration of response** *Disease free survival (DFS)*** *Time to new CLL treatment*	*72.7%* *17.2%* *34.7* *NR* *NR*	*86.1%* *36.0%* *40.2* *NR* *NR*	*<0.0001* *<0.0001* *0.0040* *0.7882* *0.0052*	*n.a.* *n.a.* *39%* *7%* *35%*

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

Table 7b First-line treatment of chronic lymphocytic leukaemia Progression-free survival according to Binet stage (ITT)

Progression-free survival (PFS)	Number of patients		Hazard Ratio (95% CI)	p-value (Wald test, not adjusted)
	FC	R-FC		
Binet A	*22*	*18*	*0.13 (0.03; 0.61)*	*0.0093*
Binet B	*257*	*259*	*0.45 (0.32; 0.63)*	*<0.0001*
Binet C	*126*	*125*	*0.88 (0.58; 1.33)*	*0.5406*

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 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 (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) *CR rates* *Duration of response ** *Disease free survival (DFS)*** *Time to new CLL treatment*	*58.0%* *13.0%* *27.6* *42.2* *34.2*	*69.9%* *24.3%* *39.6* *39.6* *NR*	*0.0034* *0.0007* *0.0252* *0.8842* *0.0024*	*n.a.* *n.a.* *31%* *-6%* *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 CLL patients have also demonstrated high overall response rates with promising PFS rates without adding relevant toxicity to the treatment.

4.1.2.4 Rheumatoid arthritis
The efficacy and safety of rituximab in alleviating the symptoms and signs of rheumatoid arthritis was demonstrated in three randomized, controlled, double-blind, multicenter studies.
Study 1 was a double blind comparative study which included 517 patients that had experienced an inadequate response or intolerance to one or more TNF inhibitor therapies. Eligible patients had severe active rheumatoid arthritis, diagnosed according to the criteria of the American College of Rheumatology (ACR). The primary endpoint was the percent of patients who achieved an ACR20 response at week 24. Patients received two 1000 mg i.v. infusions of rituximab, each following an i.v. infusion of 100 mg methylprednisolone and separated by an interval of 15 days. All patients received concomitant oral methotrexate (10-25 mg/week) and 60 mg oral prednisolone on days 2-7 and 30 mg on days 8-14 following the first infusion.
Study 2 was a randomized, double-blind, double-dummy, controlled, 3 x 3 multifactorial study which compared two different dose levels of rituximab given with or without one of two per infusional corticosteroid regimens in combination with weekly methotrexate in patients with active rheumatoid arthritis which had not responded to treatment with at least 5 other DMARDs.
Study 3 was a double-blind, double-dummy, controlled study evaluating rituximab monotherapy, and rituximab in combination with either cyclophosphamide or methotrexate in patients with active rheumatoid arthritis which had not responded to one or more prior DMARDs.
The comparator group in all three studies was weekly methotrexate (10-25mg weekly).

Disease Activity Outcomes
In all three studies, rituximab 2 x 1000 mg significantly increased the proportion of patients achieving at least a 20% improvement in ACR score compared with patients treated with methotrexate alone (Table 9). The treatment effect was similar in patients independent of age, gender, body surface area, race, number of prior treatments or disease status.
Clinically and statistically significant improvement was also noted on all individual components of the ACR response (tender and swollen joint counts, patient and physician global assessment, disability index scores (HAQ), pain assessment and CRP (mg/dL).

Table 9 Cross-Study Comparison of ACR Responses at Week 24 (ITT Population)

	ACR Response	Placebo+MTX	Rituximab+MTX
Study 1		N= 201	N= 298
	ACR20	36 (18%)	153 (51%)[1] ***
	ACR50	11 (5%)	80 (27%)[1] ***
	ACR70	3 (1%)	37 (12%)[1] ***
		N= 143	N= 185
Study 2	ACR20	45 (31%)	96 (52%)[2]
	ACR50	19 (13%)	61 (33%)[2]
	ACR70	6 (4%)	28 (15%)[2]
		N= 40	N= 40
Study 3	ACR20	15 (38%)	28 (70%)[3]
	ACR50	5 (13%)	17 (43%)[3]
	ACR70	2 (5%)	9 (23%)[3]

[1] $p \le 0.0001$; [2] $p \le 0.001$; [3] $p < 0.05$

Patients treated with rituximab in combination with methotrexate had a significantly greater reduction in disease activity score (DAS28) than patients treated with methotrexate alone (Table 10). Similarly, a good to moderate EULAR response was achieved by significantly more rituximab treated patients treated with rituximab and methotrexate compared to patients treated with methotrexate alone (Table 10).

Table 10 Cross-Study Comparison of DAS and EULAR Responses at Week 24 (ITT Population)

	Placebo+MTX	Rituximab+MTX (2 × 1g)
Study 1	Study 1	Study 1
Change in DAS28 [Mean (SD)]	-0.4 (1.2)	-1.9 (1.6)*
EULAR Response (%)		
None Moderate Good	78% 20% 2%	35% 50%* 15
Study 2	(n = 143)	(n = 185)
Mean change in DAS28 (SD)	–0.8 (1.4)	–2.0 (1.6)
None Moderate Good	61% 35% 4%	37% 40% 23%
Study 3	N=40	N=40
Change in DAS [Mean (SD)]	-1.3 (1.2)	-2.6 (1.3)
EULAR response		
None Moderate Good	50% 45% 5%	18% 63% 20%

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

Radiographic Response
Structural joint damage was assessed radiographically and expressed as change in modified total Sharp score and its components, the erosion score and joint space narrowing score.
In Study 1, conducted in patients with inadequate response or intolerance to one or more TNF inhibitor therapies, receiving rituximab in combination with methotrexate demonstrated significantly less radiographic progression than patients originally receiving methotrexate alone at 56 weeks. Of the patients originally receiving methotrexate alone, 81 % received rituximab either as rescue between weeks 16-24 or in the extension trial, before week 56. A higher proportion of patients receiving rituximab /MTX also had no erosive progression over 56 weeks (Table 11)

Table 11 Radiographic outcomes at 1 year (mITT population)

	Placebo+MTX	Rituximab+MTX (2 × 1000mg)
Study 1	(n = 184)	(n = 273)
Mean Change from Baseline:		
Modified Total Sharp score	2.31	1.00*
Erosion Score	1.32	0.59*
Joint Space narrowing score	0.99	0.41**
Proportion of patients with no radiographic change	46%	53%
Proportion of patients with no erosive change	52%	61%*

150 patients originally randomized to placebo + MTX in Study 1 received at least one course of RTX + MTX by one year * p <0 05, ** p < 0,001, Inhibition of the rate of progressive joint damage was also observed long term. Radiographic analysis at 2 years in study 1 demonstrated significantly reduced progression of structural joint damage in patients receiving rituximab in combination with methotrexate compared to methotrexate alone as well as a significantly higher proportion of patients with no progression of joint damage over the 2 year period.

Physical function and quality of life outcomes
Significant reductions in disability index (HAQ-DI) and fatigue (FACIT-Fatigue) scores were observed in patients treated with rituximab compared to patients treated with methotrexate alone. The proportions of rituximab treated patients showing a minimal clinically important difference (MCID) in HAQ-DI (defined as an individual total score decrease of >0.22) was also higher than among patients receiving methotrexate alone (Table 12).
Significant improvement in health related quality of life was also demonstrated with significant improvement in both the physical health score (PHS) and mental health score (MHS) of the SF-36.
Further, a significantly higher proportion of patients achieved MCIDs for these scores (Table 12).

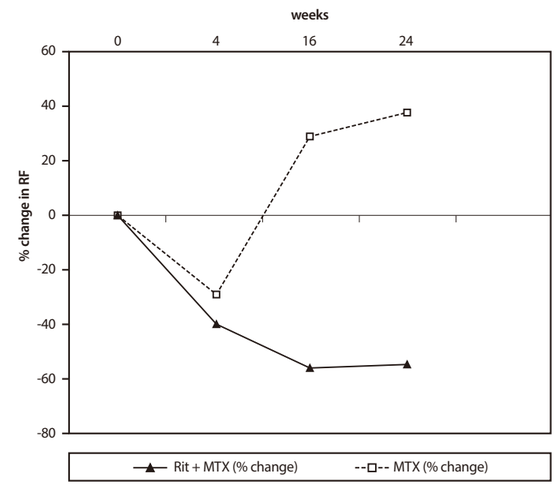
Table 12 Physical Function and Quality of Life outcomes at week 24 in study 1

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

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

Laboratory Evaluations
A total of 54/990 (5.5%) patients with rheumatoid arthritis tested positive for HACA in clinical studies. The emergence of HACA was not associated with clinical deterioration or with an increased risk of reactions to subsequent infusions in these patients.
In rheumatoid factor (RF) positive patients, marked decreases were observed in rheumatoid factor concentrations following treatment with rituximab in all three studies (range 45-64%, Figure 1).

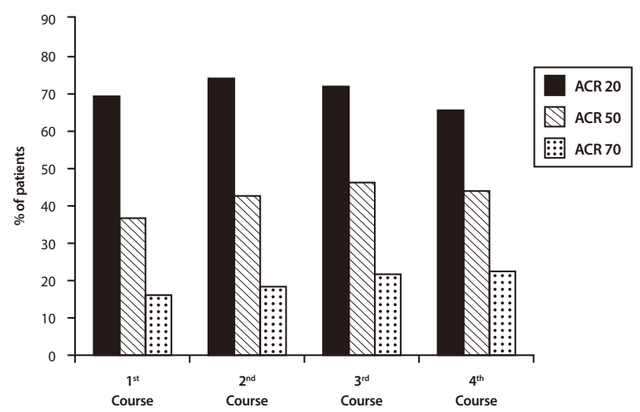
Figure 1 Percentage Change in Total RF Concentration Over Time in Study 1 (ITT Population, RF-Positive Patients)



Plasma total immunoglobulin concentrations, total lymphocytes counts, and white cells generally remained within normal limits following rituximab treatment, with the exception of a transient drop in white cells counts over the first four weeks following therapy. Titers of Ig G antigen specific antibody to mumps, rubella, varicella, tetanus toxoid, influenza and streptococcus pneumococci remained stable over 24 weeks following exposure to rituximab in rheumatoid arthritis patients.
Effects of rituximab on a variety of biomarkers was evaluated in patients enrolled into Study 3. This substudy evaluated the impact of a single treatment course of rituximab on levels of biochemical markers, including markers of inflammation [Interleukin 6, C Reactive protein, Serum amyloid type A protein, Protein S100 isotypes A8 and A9], autoantibody (RF and anti-cyclic citrullinated peptide immunoglobulin) production and bone turnover [osteocalcin and procollagen 1 N terminal peptide (P1NP). Rituximab treatment, whether as monotherapy or in combination with methotrexate or cyclophophamide reduced the levels of inflammatory markers significantly, relative to methotrexate alone, over the first 24 weeks of follow-up. Levels of markers of bone turnover, osteocalcin and P1NP, increased significantly in the rituximab groups compared to methotrexate alone.

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

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



120-minute infusion rate study (ML25641)
In a multi-center, open-label single-arm trial, 351 patients with moderate-to-severe active RA, who had an inadequate response to at least one TNF inhibitor and were receiving MTX, were to receive 2 courses of rituximab treatment. Patients who were naïve to prior rituximab therapy (n=306) and those who had received 1 to 2 prior courses of rituximab 6-9 months prior to baseline (n=45), were eligible for enrollment.
Patients received 2 courses of rituximab 2 x 1000mg + MTX treatment with the first course administered on Days 1 and 15 and the second course six-months later on Days 168 and 182. The first infusion of the first course (Day 1 infusion) was administered over a 4.25-hour period. The second infusion of the first course (Day 15 infusion) and both infusions in the second course (Day 168 and 182 infusions) were administered over 120 minutes. Any patient experiencing a serious infusion-related reaction (IRR) with any infusion was withdrawn from the study. In this study, an infusion-related reaction (IRR) was defined as any adverse event that occurred during or within 24 hours following the infusion of rituximab and met pre-specified criteria for adverse event terms for IRRs. IRRs were defined as serious if they met one of the following seriousness criteria: fatal, life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, were medically significant.
The primary objective of this study was to assess the safety of administering the second infusion of the first study course of rituximab over 120 minutes.

The incidence of IRRs at Day 15 was 6.5% (95% CI [4.1%-9.7%]) consistent with the rate observed historically. There were no serious IRRs observed. Data observed for the infusions on Days 168 and 182 (120-minute infusion) demonstrates a low incidence of IRRs, similar to the rate observed historically, with no serious IRRs occurring. (see section 3.8 Undesirable Effect)

4.2 Pharmacokinetic Properties

4.2.1 Distribution and Elimination

Non-Hodgkin's Lymphoma

Pharmacokinetic studies performed in a phase I study in which patients (N=15) with relapsed B–cell lymphoma were given single doses of rituximab at 10, 50, 100 or 500 mg/m^2 indicated that serum levels and half-life of rituximab were proportional to dose.

In a cohort of 14 patients among the 166 patients with relapsed or chemoresistant low-grade or follicular non-Hodgkin's lymphoma enrolled in the phase III pivotal trial and given rituximab 375 mg/m^2 as an i.v. infusion for 4 weekly doses, the mean serum half-life was 76.3 hours (range, 31.5 to 152.6 hours) after the first infusion and 205.8 hours (range, 83.9 to 407.0 hours) after the fourth infusion. The mean C_{max} after the first and fourth infusion were 205.6 ± 59.5 µg /ml and 464.7 ± 119.0 µg /ml, respectively. The mean plasma clearance after the first and fourth infusion was 0.0382 ± 0.0182 l/h and 0.0092 ± 0.0033 l/h, respectively.

However, variability in serum levels was large. Rituximab serum concentrations were statistically significantly higher in responding patients than in non-responding patients just prior to and after the fourth infusion and post-treatment. Serum concentrations were negatively correlated with tumor burden and the number of circulating B cells at baseline. Typically, rituximab was detectable for 3 – 6 months after administration of the last infusion.

Distribution and elimination have not been extensively studied in patients with DLCL, but available data indicate that serum levels of rituximab in DLCL patients are comparable to those in patients with low-grade or follicular NHL following treatment with similar doses.

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 µg/mL (range, 97 – 764 µg/mL) after the fifth 500 mg/m^2 infusion.

Rheumatoid Arthritis

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

The pharmacokinetics of rituximab were assessed following two IV doses of 500 mg and 1000 mg on Days 1 and 15 in four studies. In all these studies, rituximab pharmacokinetics were dose proportional over the limited dose range studied. Mean C_{max} for serum rituximab following first infusion ranged from 157 to 171 µg/ml for 2 x 500 mg dose and ranged from 298 to 341 µg/ml for 2 x 1000 mg dose.

Following second infusion, mean C_{max} ranged from 183 to 198 µg/ml for the 2 × 500 mg dose and ranged from 355 to 404 µg/ml for the 2 × 1000 mg dose. Mean terminal elimination half-life ranged from 15 to 16 days for the 2 x 500 mg dose group and 17 to 21 days for the 2 × 1000 mg dose group. Mean C_{max} was 16 to 19% higher following second infusion compared to the first infusion for both doses.

The pharmacokinetics of rituximab were assessed following two IV doses of 500 mg and 1000 mg upon re-treatment in the second course. Mean C_{max} for serum rituximab following first infusion was 170 to 175 µg/ml for 2 x 500 mg dose and 317 to 370 µg/ml for 2 x 1000 mg dose. C_{max} following second infusion, was 207 µg/ml for the 2 x 500 mg dose and ranged from 377 to 386 µg/ml for the 2 x 1000 mg dose. Mean terminal elimination half-life after the second infusion, following the second course, was 19 days for 2 x 500 mg dose and ranged from 21 to 22 days for the 2 x 1000 mg dose. PK parameters for rituximab were comparable over the two treatment courses.

4.2.2 Pharmacokinetics in Special Populations

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

5. PHARMACEUTICAL PARTICULARS

5.1 List of Excipients

Sodium citrate
Polysorbate 80
Sodium chloride
Water for injection

5.2 Incompatibilities

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

5.3 Stability

Store vials at 2 - 8 °C. Protect vials from direct sunlight.

Prepared infusion solutions of Truxima® are stable for 12 hours at room temperature stored at or below 30°C. If necessary, the prepared solutions may be stored in the refrigerator (at 2 - 8 °C) and are then chemically stable for up to 24 hours. As Truxima® contains no antimicrobial preservative, it is essential to ensure that the prepared solutions remain sterile.

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

5.4 Special Remarks

5.4.1 Instructions for Use, Handling and Disposal

Truxima® is a clear, colourless liquid supplied in sterile, preservative-free, non-pyrogenic single-dose vials.

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.

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.

5.4.2 Disposal of unused/expired medicines

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

6. PACKS

Vials of 10 ml (10 mg/ml)	2
Vial of 50 ml (10 mg/ml)	1

7. PRODUCT LICENSE HOLDER / PRODUCT REGISTRANT

Celltrion Healthcare Singapore Private Limited.
65 CHULIA STREET
#41-02 OCBC Centre,
Singapore 049513

Current at August 2021