1. NAME OF THE MEDICINAL PRODUCT

RUXIENCE (Rituximab), Concentrate for Solution for Infusion, 100 mg/10 mL
RUXIENCE (Rituximab), Concentrate for Solution for Infusion, 500 mg/50 mL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

RUXIENCE (Rituximab), Concentrate for Solution for Infusion, 100 mg/10 mL

Each mL contains 10 mg of rituximab.
Each vial contains 100 mg/10 mL of rituximab.

RUXIENCE (Rituximab), Concentrate for Solution for Infusion, 500 mg/50 mL

Each mL contains 10 mg of rituximab.
Each vial contains 500 mg/50 mL of rituximab.

Rituximab is a genetically engineered chimeric mouse/human monoclonal antibody representing a glycosylated immunoglobulin with human IgG1 constant regions and murine light-chain and heavy-chain variable region sequences. The antibody is produced by mammalian (Chinese hamster ovary) cell suspension culture and purified by affinity chromatography and ion exchange, including specific viral inactivation and removal procedures.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear to slightly opalescent, colourless to pale brownish-yellow liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Non-Hodgkin's lymphoma (NHL)

RUXIENCE is indicated for the treatment of:

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

- previously untreated patients with stage III-IV follicular lymphoma in combination with cyclophosphamide, vincristine and prednisolone (CVP) chemotherapy.

- patients with relapsed or chemoresistant indolent B-cell non-Hodgkin's lymphomas.

RUXIENCE maintenance therapy is indicated for the treatment of follicular lymphoma patients responding to induction therapy.

Chronic lymphocytic leukaemia (CLL)

RUXIENCE 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

RUXIENCE 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.

4.2 Posology and method of administration

General

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

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

The safety and efficacy of alternating or switching between RUXIENCE and products that are biosimilar but not deemed interchangeable to RUXIENCE has not been established. Therefore, the benefit/risk of alternating or switching need to be carefully considered.

Premedication and prophylactic medications

Premedication consisting of an analgesic/anti-pyretic (e.g. paracetamol) and an antihistaminic drug (e.g. diphenhydramine), should always be given before each administration of RUXIENCE. Premedication with corticosteroids should also be considered.

Premedication with glucocorticoids should be considered if RUXIENCE is not given in combination with glucocorticoid-containing chemotherapy for treatment of non-Hodgkin's lymphoma.

Patients should be closely monitored for the onset of cytokine release syndrome (see section 4.4). Patients who develop evidence of severe reactions, especially severe dyspnoea, 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 4.8) usually respond to a reduction in the rate of infusion. The infusion rate may be increased upon improvement of symptoms.

Dosage adjustments during treatment

No dose reductions of RUXIENCE are recommended. When RUXIENCE is given in combination with CVP chemotherapy, standard dose reductions for the chemotherapeutic medicinal products should be applied.

Method of administration

The prepared RUXIENCE solution should be administered as an intravenous infusion through a dedicated line. It must not be administered as an intravenous injection or bolus infusion.

Infusion rate

First intravenous 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 intravenous infusions

Subsequent infusions of RUXIENCE 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.

Standard dosage

Low-grade or follicular non-Hodgkin's lymphoma

Initial treatment

- Monotherapy

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

- Combination therapy

  The recommended dosage of RUXIENCE 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 intravenous administration of the corticosteroid component of CVP. RUXIENCE has shown acceptable safety in combination with other chemotherapies e.g. CHOP.

Re-treatment following relapse

Patients who have responded to RUXIENCE initially have been treated again with RUXIENCE at a dose of 375 mg/m^2 body surface area, administered as an intravenous infusion once weekly for 4 weeks (see section 5.1, Re-treatment, weekly for 4 doses).

Maintenance treatment

Previously untreated follicular lymphoma

The recommended dose of RUXIENCE 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 RUXIENCE 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

RUXIENCE should be used in combination with CHOP chemotherapy. The recommended dosage of RUXIENCE is 375 mg/m^2 body surface area, administered on day 1 of each chemotherapy cycle after intravenous administration of the corticosteroid component of CHOP. The other components of CHOP (cyclophosphamide, doxorubicin and vincristine) should be given after the administration of RUXIENCE. Safety and efficacy of RUXIENCE 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 x 10^9/L, it is recommended to administer prednisone/prednisolone 100 mg intravenous shortly before infusion with RUXIENCE to decrease the rate and severity of acute infusion reactions and/or cytokine release syndrome.

The recommended dosage of RUXIENCE 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 (see Method of administration, Infusion rate).

Rheumatoid arthritis

A course of RUXIENCE consists of two 1000 mg intravenous infusions. The recommended dosage of RUXIENCE is 1000 mg by intravenous infusion followed by a second 1000 mg intravenous infusion two weeks later (see Method of administration, Infusion rate).

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 re-treatment. The efficacy and safety of further courses is comparable to the first course (see sections 4.8, Experience from rheumatoid arthritis and 5.1, Clinical/efficacy Studies, Chronic lymphocytic leukaemia).

Rheumatoid arthritis patients should receive treatment with 100 mg intravenous methylprednisolone 30 minutes prior to RUXIENCE to decrease the rate and severity of acute infusion reactions (see section 4.4).

Alternative subsequent, faster, infusions schedule (rheumatoid arthritis only)

In rheumatoid arthritis, with a dose of 1000 mg RUXIENCE, 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 4 hours 15 minutes for the first infusion and 3 hours 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 RUXIENCE 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 250 mg/h for the first 30 minutes and then 600 mg/h 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 hours.

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

Paediatric use

The safety and efficacy of rituximab in children and adolescents (<18 years) have not been established.

Hypogammaglobulinaemia has been observed in paediatric patients treated with rituximab, in some cases severe and requiring long-term immunoglobulin substitution therapy. The consequences of long-term B-cell depletion in paediatric patients are unknown.

Geriatric use

No dose adjustment is required in patients aged ≥65 years of age.

4.3 Contraindications

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

Active, severe infections (see section 4.4).

Patients in a severely immunocompromised state.

4.4 Special warnings and precautions for use

General

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

Non-Hodgkin's lymphoma 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 reactions.

This set of reactions which includes syndrome of cytokine release, tumour lysis syndrome and anaphylactic and hypersensitivity reactions are described below.

Severe infusion-related reactions (IRRs) with fatal outcome have been reported during post-marketing use of the rituximab intravenous formulation. Severe IRRs usually manifested within 30 minutes to 2 hours after starting the first rituximab intravenous infusion. They were characterised by pulmonary events and included, in some cases, rapid tumour lysis and features of tumour lysis syndrome in addition to fever, chills, rigors, hypotension, urticaria, angioedema and other symptoms (see sections 4.4 and 4.8).

Severe cytokine release syndrome is characterised by severe dyspnoea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. This syndrome may be associated with some features of tumour lysis syndrome such as hyperuricaemia, hyperkalaemia, hypocalcaemia, hyperphosphataemia, acute renal failure, elevated lactate dehydrogenase (LDH) and may be associated with acute respiratory failure and death.

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 intravenous 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 intravenous 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. In contrast to cytokine release syndrome, true hypersensitivity reactions typically occur within minutes after starting infusion. Medicinal products for the treatment of hypersensitivity reactions, e.g. epinephrine (adrenaline), antihistamines and glucocorticoids, should be available for immediate use in the event of a hypersensitivity reaction to rituximab. Clinical manifestations of anaphylaxis may appear similar to clinical manifestations of the cytokine release syndrome (described above). Reactions attributed to hypersensitivity have been reported less frequently than those attributed to cytokine release.

Infusion-related adverse reactions of all kinds have been observed in 77% of patients treated with rituximab (including cytokine release syndrome accompanied by hypotension and bronchospasm in 10% of patients) (see section 4.8). These symptoms are usually reversible with interruption of rituximab infusion and administration of an anti-pyretic, an antihistaminic, and, occasionally, oxygen, intravenous saline or bronchodilators, and glucocorticoids if required. Please see cytokine release syndrome above for severe reactions.

Pulmonary events

Pulmonary events have included hypoxia, pulmonary infiltrates, and acute respiratory failure. Some of these events have been preceded by severe bronchospasm and dyspnoea. In some cases, symptoms worsened over time, while in others initial improvement was followed by clinical deterioration. Therefore, patients experiencing pulmonary events or other severe infusion-related symptoms should be closely monitored until complete resolution of their symptoms occurs. Patients with a history of pulmonary insufficiency or those with pulmonary tumour infiltration may be at greater risk of poor outcome and should be treated with increased caution. Acute respiratory failure may be accompanied by events such as pulmonary interstitial infiltration or oedema, visible on a chest x-ray. The syndrome usually manifests itself within one or two hours of initiating the first infusion. Patients who experience severe pulmonary events should have their infusion interrupted immediately (see section 4.2) 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. hyperuricaemia, hyperkalaemia, hypocalcaemia, hyperphosphataemia, acute renal failure, elevated LDH) consistent with tumour lysis syndrome (TLS) have been reported to occur after the first rituximab infusion in patients with high numbers of circulating malignant lymphocytes. Prophylaxis for TLS should be considered for patients at risk of developing rapid tumour lysis (e.g. patients with a high tumour burden or with a high number (>25 x 10^9/L) of circulating malignant cells such as patients with CLL and mantle cell lymphoma). These patients should be followed closely, and appropriate laboratory monitoring performed.

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

RUXIENCE infusion should be administered in an environment where full resuscitation facilities are immediately available, and under the close supervision of an experienced oncologist/haematologist.

Cardiovascular

Since hypotension may occur during rituximab administration, consideration should be given to withholding antihypertensive medications 12 hours prior to and throughout RUXIENCE infusion. 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 and/or cardiotoxic chemotherapy should be monitored closely.

Monitoring of blood counts

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

Consideration should be given to the need for regular full blood counts, including platelet counts, during monotherapy with RUXIENCE. When RUXIENCE 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. RUXIENCE should not be administered to patients with an active, severe infection (e.g. tuberculosis, sepsis and opportunistic infections) (see section 4.3).

The following 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 John Cunningham (JC) virus (progressive multifocal leukoencephalopathy (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.

Physicians should exercise caution when considering the use of RUXIENCE in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection (see section 4.8).

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 RUXIENCE. 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 RUXIENCE. 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, haematological 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.

Progressive multifocal leukoencephalopathy

Very rare cases of progressive multifocal leukoencephalopathy (PML) have been reported during post-marketing use of rituximab in NHL and CLL (see section 4.8). The majority of patients had received rituximab in combination with chemotherapy or as part of a haematopoietic stem cell transplant.

Use of rituximab 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, cerebrospinal fluid (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 RUXIENCE 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.

Skin reactions

Severe skin reactions such as Toxic Epidermal Necrolysis and Stevens-Johnson syndrome, some with fatal outcome, have been reported (see section 4.8). In case of such an event with a suspected relationship to rituximab, treatment should be permanently discontinued.

Immunization

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

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

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

Rheumatoid arthritis patients

Infusion-related reactions

Rituximab is associated with infusion-related reactions (IRRs), which may be related to release of cytokines and/or other chemical mediators. Premedication with intravenous glucocorticoid significantly reduced the incidence and severity of these events and should be administered prior to RUXIENCE treatment (see sections 4.2 and 4.8).

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 4.8). 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, intravenous 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 intravenous administration of proteins to patients. Medicinal products for the treatment of hypersensitivity reactions, e.g. epinephrine, antihistamines and glucocorticoids, should be available for immediate use in the event of an allergic reaction during administration of RUXIENCE.

Cardiovascular

Since hypotension may occur during rituximab infusion, consideration should be given to withholding anti-hypertensive medications 12 hours prior to the RUXIENCE 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 rituximab and the knowledge that B-cells play an important role in maintaining normal immune response, patients may have an increased risk of infection following rituximab therapy. RUXIENCE should not be administered to patients with an active infection or severely immunocompromised patients (e.g. where levels of CD4 or CD8 are very low). Physicians should exercise caution when considering the use of rituximab in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection (see section 4.8). Patients who develop infection following RUXIENCE 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 section 4.4).

Hepatitis B infections

Cases of hepatitis B reactivation including those with a fatal outcome, have been reported in rheumatoid arthritis patients receiving rituximab.

Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with RUXIENCE. 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 RUXIENCE. 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 4.8). In case of such an event with a suspected relationship to RUXIENCE, treatment should be permanently discontinued.

Progressive multifocal leukoencephalopathy

Cases of fatal progressive multifocal leukoencephalopathy (PML) have been reported following use of rituximab for the treatment of autoimmune diseases (including rheumatoid arthritis). 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 patients should, if possible, be brought up-to-date with all immunizations in agreement with current immunization guidelines prior to initiating RUXIENCE therapy and follow local/national guidance for adult vaccination against infectious disease. Vaccinations should be completed at least 4 weeks prior to first administration of RUXIENCE.

The safety of immunization with live viral vaccines following rituximab therapy has not been studied. Therefore, vaccination with live virus vaccines is not recommended whilst receiving RUXIENCE or whilst peripherally B-cell depleted.

Patients treated with RUXIENCE may receive non-live vaccinations. However, response rates to non-live vaccines may be reduced. In a randomised study, patients with rheumatoid arthritis 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 rituximab therapy, these should be completed at least 4 weeks prior to commencing the next course of rituximab.

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

Methotrexate (MTX)-naïve populations

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

Concomitant/sequential use of other disease-modifying anti-rheumatic drugs (DMARDs)

The concomitant use of RUXIENCE 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 rituximab therapy.

Malignancy

Immunomodulatory drugs may increase the risk of malignancy. Available data do not suggest an increased risk of malignancy for rituximab used in autoimmune indications beyond the malignancy risk already associated with the underlying autoimmune condition.

Paediatric use

The safety and efficacy of rituximab in children and adolescents (<18 years) have not been established.

Hypogammaglobulinaemia has been observed in paediatric patients treated with rituximab, in some cases severe and requiring long-term immunoglobulin substitution therapy. The consequences of long-term B-cell depletion in paediatric patients are unknown.

Geriatric use

No dose adjustment is required in patients aged ≥65 years of age.

Renal impairment

The safety and efficacy of rituximab in patients with renal impairment have not been established.

Hepatic impairment

The safety and efficacy of rituximab in patients with hepatic impairment have not been established.

4.5 Interaction with other medicinal products and other forms of interaction

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

In CLL patients, co-administration with rituximab did not appear to have an effect on the pharmacokinetics of fludarabine or cyclophosphamide. In addition, there was no apparent effect of fludarabine and cyclophosphamide on the pharmacokinetics of rituximab.

Co-administration with methotrexate had no effect on the pharmacokinetics of rituximab in rheumatoid arthritis patients.

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

In the rheumatoid arthritis clinical trial program, 373 rituximab-treated patients received subsequent therapy with other DMARDs, of whom 240 received a biologic DMARD. In these patients the rate of serious infection while on rituximab (prior to receiving a biologic DMARD) was 6.1 per 100 patient years compared to 4.9 per 100 patient years following subsequent treatment with the biologic DMARD.

4.6 Fertility, pregnancy and lactation

Females and males of reproductive potential

Fertility

No preclinical fertility studies have been conducted.

Contraception

Due to the long retention time of rituximab in B-cell depleted patients, women of childbearing age must employ effective contraceptive methods during and for 12 months after treatment with RUXIENCE.

Animal data

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

Pregnancy

IgG immunoglobulins are known to cross the placental barrier.

B-cell levels in human neonates following maternal exposure to rituximab have not been studied in clinical trials. There are no adequate and well-controlled data from studies in pregnant women, however transient B-cell depletion and lymphocytopenia have been reported in some infants born to mothers exposed to rituximab during pregnancy. For these reasons RUXIENCE should not be administered to pregnant women unless the possible benefit outweighs the potential risk.

Lactation

There are limited data on the presence of rituximab in human milk and the effect on the breastfed child, and there are no data on the effect on milk production. Rituximab is detected in the milk of lactating cynomolgus monkeys. Maternal IgG is present in human breast milk. Rituximab has also been reported to be excreted at low concentrations in human breast milk. Given that the clinical significance of this finding for children is not known, advise women not to breastfeed during treatment with RUXIENCE and for 6 months after the last dose due to the potential of serious adverse reactions in breastfed children.

4.7 Effects on ability to drive and use machines

Rituximab has no or negligible effect on the ability to drive and use machines.

4.8 Undesirable effects

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

Summary of the safety profile

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 frequently reported or observed serious adverse drug reactions were:
- Infusion-related reactions (including cytokine release syndrome, tumour lysis syndrome) (see section 4.4).
- Infections (see section 4.4).
- Cardiovascular events (see section 4.4).

Other serious ADRs reported include hepatitis B reactivation and PML (see section 4.4).

Tabulated list of adverse reactions

The frequencies of ADRs reported with rituximab alone or in combination with chemotherapy are summarised in Table 1 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), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data). The ADRs identified only during post-marketing surveillance, and for which a frequency could not be estimated, are listed under "not known".

Table 1 ADRs reported in clinical trials or during post-marketing 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,		Serious viral infection[2]		

		[+]acute bronchitis, [+]sinusitis, hepatitis B[1]				
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]
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 oedema, face oedema, increased LDH, hypocalcaemia				
Psychiatric disorders			Depression, nervousness			
Nervous system disorders		Paraesthesia, 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[4,6], 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, diarrhoea, 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 National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)) reactions. Only the highest frequency observed in the trials is reported.

[1] Includes reactivation and primary infections; frequency based on rituximab in combination with fludarabine and cyclophosphamide (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.

Further information on selected, serious adverse drug reactions

Administration-related reactions

Signs and symptoms suggestive of an infusion-related reaction (IRR) were reported in more than 50% of patients in clinical trials, and were predominantly seen during the first infusion, 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 tumour lysis syndrome.

Severe IRRs (such as bronchospasm, hypotension) occurred in up to 12% of the cases. Additional reactions reported in some cases were myocardial infarction, atrial fibrillation, pulmonary oedema and acute reversible thrombocytopenia. Exacerbations of pre-existing cardiac conditions such as angina pectoris or congestive heart failure or severe cardiac 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.

Localised candida infections as well as Herpes zoster were reported at a higher incidence in the rituximab-containing arm of randomised studies. Severe infections were reported in about 4% of patients treated with rituximab monotherapy. Higher frequencies of infections overall, including grade 3 or 4 infections, were observed during rituximab maintenance treatment up to 2 years when compared to observation. There was no cumulative toxicity in terms of infections reported over a 2-year treatment period. In addition, other serious viral infections either new, reactivated or exacerbated, some of which were fatal, have been reported with rituximab treatment. The majority of patients had received rituximab in combination with chemotherapy or as part of a haematopoietic stem cell transplant. Examples of these serious viral infections are infections caused by the herpes viruses (Cytomegalovirus, Varicella Zoster Virus and Herpes Simplex Virus), JC virus (progressive multifocal leukoencephalopathy (PML)) and hepatitis C virus. Cases of fatal PML that occurred after disease progression and re-treatment have also been reported in clinical trials. 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% in 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 re-treatment (see section 4.4).

Haematologic 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.

During the treatment course in studies with rituximab in combination with chemotherapy, grade 3/4 leucopenia (rituximab in combination with cyclophosphamide, doxorubicin, vincristine, prednisolone (R-CHOP) 88% vs. CHOP 79%, R-FC 23% vs. FC 12%), neutropenia (rituximab in combination with cyclophosphamide, vincristine, and prednisolone (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).

IgG levels

In the clinical trial evaluating rituximab maintenance treatment in relapsed/refractory follicular lymphoma, median IgG levels were below the lower limit of normal (LLN) (<7 g/L) after induction treatment in both the observation and the rituximab groups. In the 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).

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% R-FC, 3% FC).

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

Respiratory system

Respiratory failure/insufficiency and pulmonary infiltrates in the context of infusion-related reactions (see section 4.4). 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.

Gastrointestinal disorders

Gastrointestinal perforation in some cases leading to death has been observed in patients receiving rituximab for treatment of Non-Hodgkin's lymphoma (NHL). In the majority of these cases, rituximab was administered with chemotherapy.

Skin and subcutaneous tissue disorders

Toxic Epidermal Necrolysis and Stevens-Johnson syndrome, some with fatal outcome, have been reported very rarely.

Subpopulations

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).

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.

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 with monotherapy
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).

Experience from rheumatoid arthritis

Summary of the safety profile

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 summarised 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 4.4).

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.

Tabulated list of adverse reactions

Events are listed in Table 2. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) 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 IRRs. 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 4.4) 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 post-marketing 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	[3]Infusion-related reactions (hypertension, nausea, rash, pyrexia, pruritus, urticaria, throat irritation, hot flush, hypotension, rhinitis, rigors, tachycardia, fatigue, oropharyngeal pain, peripheral oedema, erythema)		[3]Infusion-related reactions (generalised oedema, bronchospasm wheezing, laryngeal oedema, angioneurotic oedema, generalised pruritis, anaphylaxis, anaphylactoid reaction)		
General disorders and administration site conditions					
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.

Further information on selected adverse drug reactions

Infusion-related reactions

The most frequent ADRs following receipt of rituximab in RA clinical studies were infusion-related reactions (IRRs) (refer to Table 2). Among the 3189 patients treated with rituximab, 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 declined 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 oedema, 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 4.4).

In a study designed to evaluate the safety of a 120-minute rituximab infusion in patients with RA, patients with moderate-to-severe active RA who did not experience a serious 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 IRRs were consistent with that observed historically. No serious IRRs were observed (see section 5.1, 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 intravenous 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.

4.9 Overdose

Limited experience with doses higher than the approved intravenous doses of rituximab is available from clinical trials in humans. The highest intravenous dose of rituximab tested in humans to date is 5000 mg (2250 mg/m^2), tested in a dose escalation study in patients with chronic lymphocytic leukaemia. No additional safety signals were identified.

Patients who experience overdose should have immediate interruption of their infusion and be closely monitored. Consideration should be given to the need for regular monitoring of blood cell count and for increased risk of infections while patients are B-cell depleted.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 haemopoietic stem cells, pro-B-cells, normal plasma cells, or other normal tissue. The antigen is expressed on >95% of all B-cell non-Hodgkin's lymphomas (NHLs). Following antibody binding, CD20 is not internalised or shed from the cell membrane into the

environment. CD20 does not circulate in the plasma as a free antigen and, thus, does not compete for antibody binding.

Rituximab binds to the CD20 antigen on B lymphocytes and initiates immunologic reactions that mediate B-cell lysis. Possible mechanisms of cell lysis include complement-dependent cytotoxicity (CDC) 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 haematological malignancies, B-cell repletion began within 6 months of treatment returning to normal levels between 9 and 12 months after completion of therapy. In patients with rheumatoid arthritis, the duration of peripheral B-cell depletion was variable. The majority of patients received further treatment prior to full B-cell repletion. A small proportion of patients had prolonged peripheral B-cell depletion lasting 2 years 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.

Biosimilarity

In the pharmacokinetic similarity Study B3281001 in rheumatoid arthritis (RA) subjects, median CD19-positive B-cell counts decreased at week 2 and remained decreased until week 25 (End of Trial). A majority of the observations were below the limit of quantitation. There were no notable differences observed among treatment groups in CD19-positive B-cell counts (see section 5.2).

In the extension Study B3281004, median CD19-positive B-cell counts remained suppressed from the previous treatments in Study B3281001 and showed little variation between treatment groups after treatment in Course 1. The CD19-positive B-cell counts remained depleted over the entire treatment period, including Course 2 and Course 3, independent of switching study treatment from Study B3281001, indicating that there were no notable differences between the treatments (see section 5.2).

In the comparative efficacy and safety Study B3281006 in patients with CD20-positive, low tumour burden-follicular lymphoma, there was a rapid depletion in median in CD19-positive B-cell counts following initial dosing; past the 6-month interval cell counts recovered and continued to show an increase through week 52 (end of study). Results were comparable between the 2 treatment groups (see section 5.2).

Clinical/efficacy studies

Low-grade or follicular non-Hodgkin's lymphoma

Rituximab 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 intravenous infusion weekly for four doses. The overall response rate (ORR) in the intent-to-treat (ITT) population was 48% (95% CI; 41%-56%) with a 6% complete response (CR) and a 42% partial response (PR) rate. The projected median time to progression (TTP) for responding patients was 13.0 months.

In a subgroup analysis, the ORR was higher in patients with International working group foundation (IWF) B, C, and D histologic subtypes as compared to IWF A subtype (58% vs 12%), higher in patients whose largest lesion was <5 cm vs. >7 cm in greatest diameter (53% vs. 38%), and higher in patients with chemosensitive relapse as compared to chemoresistant (defined as duration of response <3 months) relapse (50% vs 22%). ORR in patients previously treated with autologous bone marrow transplant (ABMT) was 78% versus 43% in patients with no ABMT. Neither age, sex, lymphoma grade, initial diagnosis, presence or absence of bulky disease, normal or high LDH nor presence of extranodal disease had a statistically significant effect (Fisher's exact test) on response to rituximab.

A statistically significant correlation was noted between response rates and bone marrow involvement. 40% of patients with bone marrow involvement responded compared to 59% of patients with no bone marrow involvement (p=0.0186). This finding was not supported by a stepwise logistic regression analysis in which the following factors were identified as prognostic factors: histologic type, bcl-2 positivity at baseline, resistance to last chemotherapy and bulky disease.

Initial treatment, weekly for 8 doses

In a multi-centre, single-arm study, 37 patients with relapsed or chemoresistant, low-grade or follicular B-cell NHL received 375 mg/m^2 of rituximab as intravenous infusion weekly for eight doses. The ORR was 57% (95% CI; 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 intravenous infusion weekly for four doses. The ORR was 36% (95% CI; 21%-51%; CR 3%, PR 33%) with a median TTP for responding patients of 9.6 months (range 4.5 to 26.8 months).

Re-treatment, weekly for 4 doses

In a multi-centre, single-arm study, 58 patients with relapsed or chemoresistant low-grade or follicular B-cell NHL, who had achieved an objective clinical response to a prior course of

rituximab, were re-treated with 375 mg/m^2 of rituximab as intravenous infusion weekly for four doses. Three of the patients had received two courses of rituximab before enrolment and thus were given a third course in the study. Two patients were re-treated twice in the study. For the 60 re-treatments on study, the ORR was 38% (95% CI; 26%-51%; CR 10%, PR 28%) with a projected median TTP for responding patients of 17.8 months (range 5.4-26.6). This compares favourably with the TTP achieved after the prior course of rituximab (12.4 months).

Rituximab in combination with CVP chemotherapy

Initial treatment

In an open-label randomised trial, a total of 322 previously untreated patients with follicular lymphoma were randomized to receive either CVP chemotherapy (cyclophosphamide 750 mg/m^2, vincristine 1.4 mg/m^2 up to a maximum of 2 mg on day 1, and prednisolone 40 mg/m^2/day on days 1-5) every 3 weeks for 8 cycles, or rituximab 375 mg/m^2 in combination with CVP (R-CVP). Rituximab was administered on the first day of each treatment cycle. A total of 321 patients (162 R-CVP, 159 CVP) received therapy and were analysed for efficacy.

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

Results from three other randomised trials using rituximab in combination with chemotherapy regimen other than CVP (CHOP, MCP, CHVP/Interferon-α) have also demonstrated significant improvements in response rates, time-dependent parameters as well as in overall survival. Key results from all four trials are summarised in Table 3.

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

Trial	Treatment, N	Median FU, months	ORR, %	CR, %	Median TTF/PFS/EFS months	OS rates, %
M39021	CVP, 159 R-CVP, 162	53	57 81	10 41	Median TTP: 14.7 33.6 p<0.0001	53-months 71.1 80.9 p=0.029
GLSG'00	CHOP, 205 R-CHOP, 223	18	90 96	17 20	Median TTF: 2.6 years Not reached p<0.001	18-months 90 95 p=0.016

Trial	Treatment, N	Median FU, months	ORR, %	CR, %	Median TTF/PFS/EFS months	OS rates, %
OSHO-39	MCP, 96 R-MCP, 105	47	75 92	25 50	Median PFS: 28.8 Not reached p<0.0001	48-months 74 87 p=0.0096
FL2000	CHVP-IFN, 183 R-CHVP-IFN, 175	42	85 94	49 76	Median EFS: 36 Not reached p<0.0001	42-months 84 91 p=0.029
EFS: event-free survival; TTP: time to progression or death; PFS: progression-free survival; TTF: time to treatment failure; OS rates: survival rates at the time of the analyses.						

Rituximab maintenance therapy

Previously untreated follicular lymphoma

In a prospective, open-label, international, multi-centre, phase III trial 1193 patients with previously untreated advanced follicular lymphoma received induction therapy with R-CHOP (n=881), R-CVP (n=268) or R-FCM (n=44), according to the investigators' choice. A total of 1078 patients responded to induction therapy, of which 1018 were randomised to rituximab maintenance therapy (n=505) or observation (n=513). The two treatment groups were well balanced with regards to baseline characteristics and disease status. Rituximab maintenance treatment consisted of a single infusion of rituximab at 375 mg/m^2 body surface area given every 2 months until disease progression or for a maximum period of two years.

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

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

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

	Primary analysis (median FU: 25 months)		Final analysis (median FU: 9.0 years)	
	Observation N=513	**Rituximab N=505**	**Observation N=513**	**Rituximab N=505**
Primary efficacy				
Progression-free survival (median)	NR	NR	4.06 years	10.49 years
Log-rank p-value	<0.0001		<0.0001	

Hazard ratio (95% CI) Risk reduction	0.50 (0.39, 0.64) 50%	0.61 (0.52, 0.73) 39%
Secondary efficacy		
Overall survival (median) Log-rank p-value Hazard ratio (95% CI) Risk reduction	NR NR 0.7246 0.89 (0.45, 1.74) 11%	NR NR 0.7953 1.04 (0.77, 1.40) -6%
Event-free survival (median) Log-rank p-value Hazard ratio (95% CI) Risk reduction	38 months NR <0.0001 0.54 (0.43, 0.69) 46%	4.04 years 9.25 years <0.0001 0.64 (0.54, 0.76) 36%
TNLT (median) Log-rank p-value Hazard ratio (95% CI) Risk reduction	NR NR 0.0003 0.61 (0.46, 0.80) 39%	6.11 years NR <0.0001 0.66 (0.55, 0.78) 34%
TNCT (median) Log-rank p-value Hazard ratio (95% CI) Risk reduction	NR NR 0.0011 0.60 (0.44, 0.82) 40%	9.32 years NR 0.0004 0.71 (0.59, 0.86) 39%
Overall response rate* Chi-squared test p-value Odds ratio (95% CI)	55% 74% <0.0001 2.33 (1.73, 3.15)	61% 79% <0.0001 2.43 (1.84, 3.22)
Complete response (CR/CRu) rate* Chi-squared test p-value Odds ratio (95% CI)	48% 67% <0.0001 2.21 (1.65, 2.94)	53% 67% <0.0001 2.34 (1.80, 3.03)
* At end of maintenance/observation; final analysis results based on median follow-up of 73 months. FU: follow-up; NR: not reached at time of clinical cut off; TNCT: time to next chemotherapy treatment; TNLT: time to next anti-lymphoma treatment.		

Rituximab maintenance treatment provided consistent benefit in all predefined subgroups tested: gender (male, female), age (<60 years, ≥60 years), Follicular Lymphoma International Prognostic Index (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.

Relapsed/refractory follicular NHL

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

The final efficacy analysis included all patients randomised to both parts of the study. After a median observation time of 31 months for patients randomised to the induction phase, R-CHOP significantly improved the outcome of patients with relapsed/refractory follicular NHL when compared to CHOP (see Table 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				
ORR[2)]	74%	87%	0.0003	NA
CR[2)]	16%	29%	0.0005	NA
PR[2)]	58%	58%	0.9449	NA
Secondary efficacy				
OS (median)	NR	NR	0.0508	32%
PFS (median)	19.4 mo.	33.2 mo.	0.0001	38%

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

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

The median time to new anti-lymphoma treatment was significantly longer with rituximab maintenance treatment than with observation (38.8 months vs. 20.1 months, p<0.0001, log-rank test). The risk of starting a new treatment was reduced by 50% (95% CI; 30%-64%). In patients achieving a CR/CRu (complete response unconfirmed) as best response during induction treatment, rituximab maintenance treatment significantly prolonged the median disease-free survival (DFS) compared to the observation group (53.7 vs 16.5 months, p=0.0003, log-rank test) (Table 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 vs. >0), B symptoms (absent, present), bone marrow involvement (no vs. yes), International Prognostic Index (IPI) (0-2 vs. 3-5), FLIPI score (0-1 vs. 2 vs. 3-5), number of extra-nodal sites (0-1 vs. >1), number of nodal sites (<5 vs. ≥5), number of previous regimens (1 vs. 2), best response to prior therapy (CR/PR vs. NC/PD), haemoglobin (<12 g/dL vs. ≥12 g/dL), β2-microglobulin (<3 mg/L vs. ≥3 mg/L), LDH (elevated, not elevated) except for the small subgroup of patients with bulky disease.

Diffuse large B-cell non-Hodgkin's lymphoma

In a randomised, open-label trial, a total of 399 previously untreated elderly patients (age 60 to 80 years) with diffuse large B-cell lymphoma received standard CHOP chemotherapy (cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2 up to a maximum of 2 mg on day 1, and prednisolone 40 mg/m^2/day on days 1-5) every 3 weeks for 8 cycles, or rituximab 375 mg/m^2 plus CHOP (R-CHOP). Rituximab was administered on the first day of the treatment cycle.

The final efficacy analysis included all randomized patients (197 CHOP, 202 R-CHOP), and had a median follow-up duration of approximately 31 months. The two treatment groups were well balanced in baseline characteristics and disease status. The final analysis confirmed that R-CHOP significantly increased the duration of event-free survival (the primary efficacy parameter, where events were death, relapse or progression of lymphoma, or institution of a new anti-lymphoma treatment) (p=0.0001). Kaplan Meier estimates of the median duration of event-free survival were 35 months in the R-CHOP arm compared to 13 months in the CHOP arm, representing a risk reduction of 41%. At 24 months, estimates for overall survival were 68.2% in the R-CHOP arm compared to 57.4% in the CHOP arm. A subsequent analysis of the duration of overall survival, carried out with a median follow-up duration of 60 months,

confirmed the benefit of R-CHOP over CHOP treatment (p=0.0071), representing a risk reduction of 32%.

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

In all patient subgroups (gender, age, age-adjusted IPI, Ann Arbor stage, Eastern Cooperative Oncology Group (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.

Chronic lymphocytic leukaemia

In two open-label randomized trials, a total of 817 previously untreated patients and 552 patients with relapsed/refractory CLL were randomized to receive either FC chemotherapy (fludarabine 25 mg/m^2, cyclophosphamide 250 mg/m^2, days 1-3) every 4 weeks for 6 cycles or rituximab in combination with FC (R-FC). Rituximab was administered at a dosage of 375 mg/m^2 during the first cycle one day prior to chemotherapy and at a dosage of 500 mg/m^2 on day 1 of 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) for the first-line study (Tables 7a and 7b) and 552 patients (276 R-FC, 276 FC) for the relapsed/refractory study Table 8 were analysed 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 analysed 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)	72.7%	86.1%	<0.0001	n.a.
CR rates	17.2%	36.0%	<0.0001	n.a.
Duration of response*	34.7	40.2	0.0040	39%

Disease-free survival (DFS)**	NR	NR	0.7882	7%
Time to new CLL treatment	NR	NR	0.0052	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 end-of-treatment response.
** 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 analysed 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)	58.0%	69.9%	0.0034	n.a.
CR rates	13.0%	24.3%	0.0007	n.a.
Duration of response*	27.6	39.6	0.0252	31%
Disease-free survival (DFS)**	42.2	39.6	0.8842	-6%
Time to new CLL treatment	34.2	NR	0.0024	35%

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

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

Rheumatoid arthritis

The efficacy and safety of rituximab in alleviating the symptoms and signs of rheumatoid arthritis was demonstrated in three randomised, controlled, double-blind, multi-centre 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 intravenous infusions of rituximab, each following an intravenous 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 (10-25 mg 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 C-Reactive Proteins (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]
Study 2		N=143	N=185
	ACR20	45 (31%)	96 (52%)[2]
	ACR50	19 (13%)	61 (33%)[2]
	ACR70	6 (4%)	28 (15%)[2]
Study 3		N=40	N=40

	ACR20 ACR50 ACR70	15 (38%) 5 (13%) 2 (5%)	28 (70%)[3] 17 (43%)[3] 9 (23%)[3]
[1] p≤0.0001; [2] p≤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 European League Against Rheumatism (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 x 1000 mg)**
Study 1	(N=201)	(N=298)
Change in DAS28 (Mean (SD)) EULAR Response (%)	-0.4 (1.2)	-1.9 (1.6)*
None	78%	35%
Moderate	20%	50%*
Good	2%	15%
Study 2	(N=143)	(N=185)
Mean change in DAS28 (SD) EULAR response (%)	-0.8 (1.4)	-2.0 (1.6)
None	61%	37%
Moderate	35%	40%
Good	4%	23%
Study 3	N=40	N=40
Change in DAS (Mean (SD)) EULAR response (%)	-1.3 (1.2)	-2.6 (1.3)
None	50%	18%
Moderate	45%	63%
Good	5%	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 x 1000 mg)
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 rituximab+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

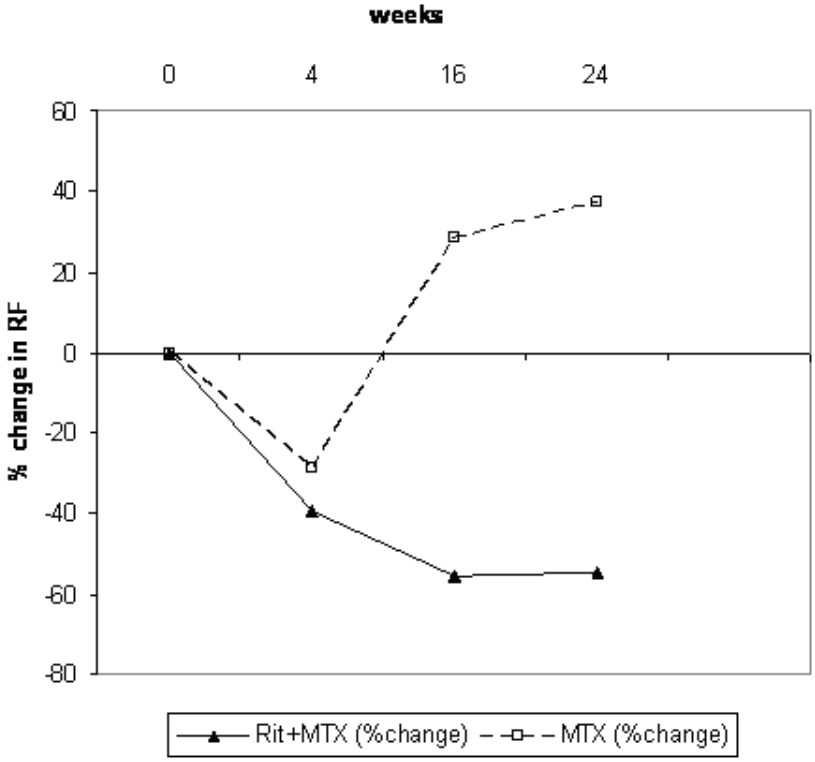
Outcome†	**Placebo+MTX**	**Rituximab+MTX (2 x 1000 mg)**
	N=201	N=298
Mean change in HAQ-DI	0.1	-0.4***
% HAQ-DI MCID	20%	51%
Mean change in FACIT-T	-0.5	-9.1***
	n=197	n=294
Mean change in SF-36 PHS	0.9	5.8***
% SF-36 PHS MCID	13%	48%***
Mean change in SF-36 MHS	1.3	4.7**
% SF-36 MHS MCID	20%	38%*
†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

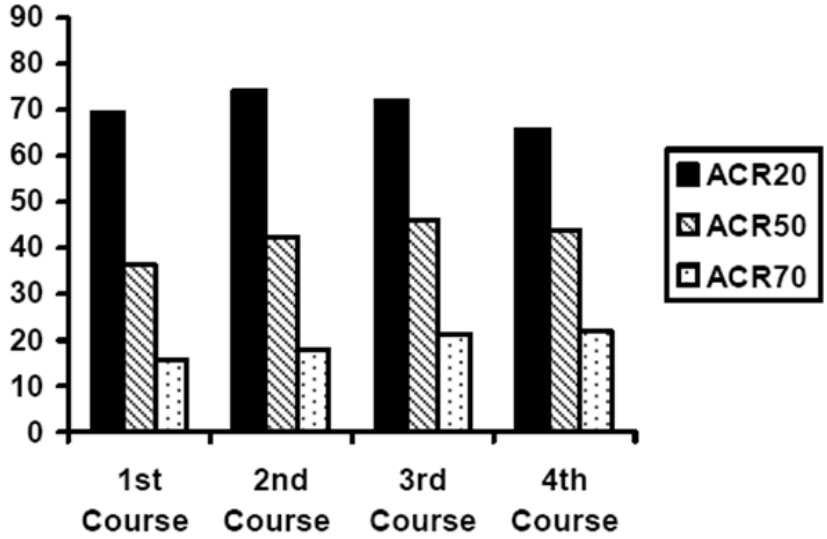
Effects of rituximab on a variety of biomarkers was evaluated in patients enrolled into Study 3. This substudy evaluated the impact of a single treatment course of rituximab on levels of biochemical markers, including markers of inflammation (Interleukin 6, C Reactive protein, Serum amyloid type A protein, 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 cyclophosphamide 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-centre, 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 enrolment.

Patients received 2 courses of rituximab 2 x 1000 mg + 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 (days 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 4.8).

RUXIENCE comparative clinical studies

The biosimilar clinical development program for RUXIENCE included a randomised, double-blind study in patients with CD20-positive, low tumour burden-follicular lymphoma in the first-line treatment setting (Study B3281006), a randomised, double-blind parallel group study in rheumatoid arthritis patients (Study B3281001), and an extension randomised double-blind extension study conducted to provide continue treatment access to patients from study B3281001 (Study B3281004).

B3281006

Study B3281006 was a randomised, double-blind study comparing the efficacy and safety of RUXIENCE (n=196) vs. MabThera (n=198) in patients with CD20-positive, low tumour burden-follicular lymphoma in the first-line treatment setting. Patients were randomised in a ratio of 1:1 to receive RUXIENCE or MabThera administered as an intravenous infusion at a dose of 375 mg/m^2 at visits 2, 3, 4, and 5 (days 1, 8, 15, and 22). The maximum dose of rituximab administered in one day was 1125 mg via intravenous infusion.

The primary objective of this trial was to compare the efficacy of RUXIENCE to MabThera when administered as a first-line treatment to patients with CD20-positive, low tumour burden-follicular lymphoma. The primary efficacy endpoint was the overall response rate (ORR) at week 26 of RUXIENCE and MabThera and is defined as the proportion of patients who achieved complete response (CR) or partial response (PR) in accordance with the revised response criteria for malignant lymphoma. Secondary endpoints included additional efficacy, safety, pharmacokinetics, pharmacodynamics, and immunogenicity.

Similarity between RUXIENCE and MabThera was statistically demonstrated for the primary efficacy endpoint, ORR, based on pre-specified equivalence criteria of -16.0% to 16.0%. The ORRs were n=148 (75.5%) for RUXIENCE and n=140 (70.7%) for MabThera. The analysis of ORR derived from central review assessments showed an estimated difference of 4.66%, with a 95% CI of (-4.16%, 13.47%), which fell entirely within the equivalence margin. The results of other secondary endpoints were comparable between the 2 treatment groups.

There were no clinically meaningful differences in efficacy, safety, or immunogenicity between RUXIENCE and MabThera in patients with CD20-positive, low tumour burden-follicular lymphoma.

B3281001 and B3281004

Study B3281001 was a 1:1:1 randomised, double-blind parallel group study in rheumatoid arthritis patients that compared the pharmacokinetics, pharmacodynamics, and safety

(including immunogenicity) of RUXIENCE, MabThera, or Rituxan. Secondary endpoints included clinical disease activity assessments.

Study B3281004 was a randomised double-blind extension study conducted in rheumatoid arthritis patients who had participated for at least 16 weeks in the B3281001 study. Patients on RUXIENCE in Study B3281001 continued to receive RUXIENCE and patients who received MabThera or Rituxan were switched to RUXIENCE. Secondary endpoints included clinical disease activity assessments.

Study B3281001 and Study B3281004 were not designed for formal statistical comparison of efficacy endpoints. The efficacy results in these studies were comparable between RUXIENCE, MabThera, and Rituxan. There were no clinically meaningful differences in safety or immunogenicity between RUXIENCE, MabThera, and Rituxan in patients with rheumatoid arthritis.

5.2 Pharmacokinetic properties

Absorption

Not applicable.

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 intravenous 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 tumour 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 intravenous 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 body surface area (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 intravenous 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 x 500 mg dose and ranged from 355 to 404 µg/mL for the 2 x 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 x 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 intravenous 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. pharmacokinetic parameters for rituximab were comparable over the two treatment courses.

Pharmacokinetics in special populations

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

RUXIENCE comparative pharmacokinetic studies

Pharmacokinetic similarity of RUXIENCE and rituximab was evaluated in 198 rheumatoid arthritis (RA) subjects in a three-arm, double-blind, randomised, (1:1:1) parallel group,

single-dose study (B3281001) comparing RUXIENCE, MabThera and Rituxan following intravenous infusion of a single 1000 mg dose on day 1 and day 15.

The 3 study drugs (RUXIENCE, MabThera, and Rituxan) exhibited a similar pharmacokinetic (PK) profile. The 90% CIs for test-to-reference ratios of C_{max}, AUC_t, and AUC_{inf} were contained within the pre-specified acceptance boundaries of 80.00% to 125.00% for the comparisons of RUXIENCE to MabThera and Rituxan, and MabThera to Rituxan. The test-to-reference ratios (90% CIs of the ratios) of adjusted geometric means of C_{max}, AUC_t, and AUC_{inf} were 105.67% (96.91%, 115.21%), 103.36% (92.81%, 115.12%), and 104.19% (92.75%, 117.06%), respectively, for the RUXIENCE to MabThera comparison; and 106.62% (97.65%, 116.41%), 101.33% (90.82%, 113.04%), and 100.45% (89.20%, 113.11%), respectively, for the RUXIENCE to Rituxan comparison. The test-to-reference ratios (90% CIs of the ratios) of adjusted geometric means of C_{max}, AUC_t, and AUC_{inf} were 100.90% (92.38%, 110.20%), 98.03% (87.83%, 109.40%), and 96.40% (85.57%, 108.60%), respectively, for the MabThera to Rituxan comparison. Overall, the study demonstrates the pharmacokinetic similarity of RUXIENCE to both MabThera and Rituxan, and of MabThera to Rituxan.

In the extension Study B3281004 for subjects with active RA who had participated for at least 16 weeks in Study B3281001 and had not received intervening treatment (i.e. in the period when the subject completed participation in Study B3281001 and sought enrolment in Study B3281004) with investigational agents or other biologics (including MabThera and Rituxan), all subjects were offered up to 3 courses (6 doses) of study treatment. A course was defined as 2 intravenous infusions (1000 mg/500 mL) of study treatment administered on days 1 and 15 of a 24-week (±8 week) course. Mean serum concentration data for RUXIENCE and MabThera indicated similar rituximab serum concentrations between the 5 treatment groups, supporting the pharmacokinetic similarity that was observed in the pharmacokinetic similarity study B3281001.

In the comparative clinical Study B3281006 in patients with CD20-positive, low tumour burden-follicular lymphoma, following 4 weekly infusions of RUXIENCE or MabThera administered at 375 mg/m^2 of body surface area (for a maximum dose of 1125 mg), mean serum concentration data for RUXIENCE and MabThera indicated similar rituximab serum concentrations between the 2 treatment groups.

5.3 Preclinical safety data

Rituximab has shown to be highly specific to the CD20 antigen on B-cells. Toxicity studies in cynomolgus monkeys have shown no other effect than the expected pharmacological depletion of B-cells in peripheral blood and in lymphoid tissue.

Developmental toxicity studies have been performed in cynomolgus monkeys at doses up to 100 mg/kg (treatment on gestation days 20-50) and have revealed no evidence of toxicity to the foetus due to rituximab. However, dose-dependent pharmacologic depletion of B-cells in the lymphoid organs of the foetuses was observed, which persisted postnatally and was accompanied by a decrease in IgG level in the newborn animals affected. B-cell counts returned to normal in these animals within 6 months of birth and did not compromise the reaction to immunization.

Standard tests to investigate mutagenicity have not been carried out, since such tests are not relevant for this molecule. No long-term animal studies have been performed to establish the carcinogenic potential of rituximab.

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

RUXIENCE preclinical safety data summary

A single-dose intravenous toxicokinetics (TK)/tolerability study with a 13-week follow-up period in cynomolgus monkeys administered RUXIENCE or rituximab-EU was conducted to further support the nonclinical similarity of RUXIENCE. In that study, the tolerability, B-cell depletion and repletion, TK, and anti-drug antibody response of RUXIENCE was similar to rituximab-EU.

A 4-week repeat dose intravenous toxicity study followed by a 13-week recovery period in cynomolgus monkeys was conducted to evaluate and to compare the potential toxicity, local tolerance, PK/TK, PD, and immunogenicity profiles between RUXIENCE and rituximab-EU at 0 and 20 mg/kg/day. Weekly administration of the test articles for 4 weeks was generally well tolerated. The predominant effect of both products was B-cell depletion followed by partial repletion during the recovery period. Overall, RUXIENCE and rituximab-EU had similar profiles in toxicity (including local tolerance), PK/TK, PD, and immunogenicity in cynomolgus monkeys.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-histidine
L-histidine hydrochloride monohydrate
Edetate disodium dihydrate
Polysorbate 80
Sucrose
Water for injection

6.2 Incompatibilities

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

6.3 Shelf life

Refer to outer carton for expiration date.

6.4 Special precautions for storage

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

Diluted medicinal product

- After aseptic dilution in sodium chloride solution

The prepared infusion solution of RUXIENCE in 0.9% sodium chloride solution is physically and chemically stable for 24 hours at 2°C-8°C plus an additional 24 hours at ≤30°C.

- After aseptic dilution in D-glucose solution

The prepared infusion solution of RUXIENCE in 5% D-glucose solution is physically and chemically stable for 24 hours at 2°C-8°C plus an additional 24 hours at ≤30°C.

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

6.5 Nature and contents of container

RUXIENCE (Rituximab), Concentrate for Solution for Infusion, 100 mg/10 mL
Clear Type I glass vials with chlorobutyl rubber stopper containing 100 mg of rituximab in 10 mL.
Pack of 1 vial.

RUXIENCE (Rituximab), Concentrate for Solution for Infusion, 500 mg/50 mL
Clear Type I glass vials with chlorobutyl rubber stopper containing 500 mg of rituximab in 50 mL.
Pack of 1 vial.

6.6 Special precautions for disposal and other handling

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

Use a sterile needle and syringe to prepare RUXIENCE. Aseptically withdraw the necessary amount of RUXIENCE, and dilute to a calculated concentration of 1 to 4 mg/mL rituximab into an infusion bag containing sterile, pyrogen-free sodium chloride 9 mg/mL (0.9%) solution for injection or 5% D-Glucose in water. For mixing the solution, gently invert the bag in order to avoid foaming. Care must be taken to ensure the sterility of prepared solutions. Since the medicinal product does not contain any anti-microbial preservative or bacteriostatic agents, aseptic technique must be observed. Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration.

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

7. PRODUCT OWNER

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