Rixathon[®]

Rituximab

Concentrate for solution for intravenous infusion

1. NAME OF THE MEDICINAL PRODUCT

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains 10 mg of rituximab. 10 ml vial: Each vial containing 100 mg of rituximab.

50 ml vial: Each vial containing 500 mg of rituximab. Rituximab is a genetically engineered chimeric mouse/human monoclonal antibody representing hamster ovary) cell suspension culture and purified by affinity chromatography and ion exchange, including specific viral inactivation and removal procedures. Excipients with known effects:

This medicinal product contains 2.3 mmol (52.6 mg) sodium per 10 mL vial. This medicinal product contains 11.5 mmol (263.2 mg) sodium per 50 mL vial. For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear, colourless to slightly yellowish liquid. Rixathon is a biosimilar medicinal product that has been demonstrated to be similar in quality safety and efficacy to the reference medicinal product Mabthera. Please be aware of any differences in the indications between the biosimilar medicinal product and the reference medicinal product. The biosimilar is not to be switched with the reference medicinal product unless specifically stated otherwise. More detailed information regarding biosimilar medicinal Rheumatoid arthritis only products is available on the website of the Ministry of Health: https://www.health.gov.il/UnitsOffice/HD/MTI/Drugs/Registration/Pages/Biosimilars.aspx

4. CLINICAL PARTICULARS

4.1 Therapeutic indications Rixathon is indicated for the following indications:

Rixathon is indicated for the treatment of patients with relapsed or refractory low-grade or follicular. B-cell non-Hodgkin's lymphoma

Rixathon is indicated for the treatment of previously untreated patients with low-grade or follicular lymphoma in combination with chemotherapy. Rixathon is indicated for the treatment of patients with CD20 positive diffuse large B-cell 4.3 Contraindications non-Hodgkin's lymphoma in combination with CHOP chemotherapy. Rixathon maintenance therapy is indicated for the treatment of follicular lymphoma patients

Hypersensitivity to the active substance or to murine proteins, or to any of the other excipients

anti-pyretic, an antihistamine, and, occasionally, oxygen, intravenous saline or bronchodilators, responding to induction therapy.

Chronic lymphocytic leukaemia (CLL) Rixathon in combination with chemotherapy is indicated for the treatment of patients with Patients in a severely immunocompromised state. are available on efficacy and safety for patients previously treated with monoclonal antibodies microscopic polyangiitis (MPA) and pemphigus vulgaris including rituximab or patients refractory to previous rituximab plus chemotherapy.

Rheumatoid arthritis Rixathon is indicated, in combination with methotrexate, to reduce signs and symptoms in Active, severe infections (see section 4.4). Patients in a severely immunocompromised state

Granulomatosis with polyangiitis and microscopic polyangiitis Rixathon, in combination with glucocorticoids, is indicated for the treatment of adult patients

with granulomatosis with polyangiitis (GPA) (Wegener's Granulomatosis (WG)) and microscopic polyangiitis (MPA). Pemphigus vulgaris (PV) Rixathon is indicated for the treatment of adult patients with moderate to severe pemphigus

4.2 Posology and method of administration

Rixathon should be administered under the close supervision of an experienced healthcare Premedication and prophylactic medications

diphenhydramine, should always be given before each administration of Rixathon. alucocorticoid- containing chemotherapy. Prophylaxis with adequate hydration and administration of uricostatics starting 48 hours prior

the rate and severity of acute infusion reactions and/or cytokine release syndrome. In patients with rheumatoid arthritis or pemphigus vulgaris, premedication with 100 mg intravenous methylprednisolone should be completed 30 minutes prior to Rixathon infusions to decrease the incidence and severity of infusion related reactions (IRRs). In patients with granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis,

methylprednisolone given intravenously for 1 to 3 days at a dose of 1000 mg per day is recommended prior to the first infusion of Rixathon (the last dose of methylprednisolone may indistinguishable from acute hypersensitivity reactions. Inisone 1 mg/kg/day (not to exceed 80 mg/day and tapered as rapidly as possible based anaphylactic and hypersensitivity reactions are described below. on clinical need) during and after Rixathon treatment.

Posology Non-Hodgkin's lymphoma Follicular non-Hodgkin's lymphoma

body surface area per cycle, for up to 8 cycles. Rixathon should be administered on day 1 of each chemotherapy cycle, after intravenous administration of the glucocorticoid component of the chemotherapy if applicable. Maintenance therapy

 Previously untreated follicular lymphoma previously untreated follicular lymphoma who have responded to induction treatment is: 375 mg/m² 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 Relapsed/refractory follicular lymphoma

The recommended dose of Rixathon used as a maintenance treatment for patients with resolved or ruled out. 75 mg/m² body surface area once every 3 months (starting 3 months after the last dose of resulted in repeated severe cytokine release syndrome. nduction therapy) until disease progression or for a maximum period of two years.

 Relapsed/refractory follicular lymphoma an intravenous infusion once weekly for four weeks. For retreatment with Rixathon monotherapy for patients who have responded to previous with rituximab (including cytokine release syndrome accompanied by hypotension and first administration of Rixathon.

infusion once weekly for four weeks (see section 5.1). Diffuse large B cell non-Hodgkin's lymphoma

Dose adjustments during treatment No dose reductions of Rixathon are recommended. When Rixathon is given in combination

should be applied Chronic lymphocytic leukaemia The recommended dosage of Rixathon in combination with chemotherapy for previously Since hypotension may occur during rituximab administration, consideration should be given untreated and relapsed/refractory patients is 375 mg/m² body surface area administered on

day 0 of the first treatment cycle followed by 500 mg/m2 body surface area administered on day 1 of each subsequent cycle for 6 cycles in total. The chemotherapy should be given after Cardiac disorders Rixathon infusion. Rheumatoid arthritis

A course of Rixathon consists of two 1000 mg intravenous infusions. The recommended dosage of Rixathon is 1000 mg by intravenous infusion followed by a second 1000 mg Haematological toxicities intravenous infusion two weeks later. Subsequent courses should be administrated every 24 weeks or based on clinical evaluation, but not sooner than every 16 weeks. Available data suggest that clinical response is usually achieved within 16 - 24 weeks of an

initial treatment course. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within this time period. Granulomatosis with polyangiitis and microscopic polyangiitis The recommended dosage of Rixathon for induction of remission therapy of granulomatosis

with polyangiitis and microscopic polyangiitis is 375 mg/m² body surface area, administered as an intravenous infusion once weekly for 4 weeks (four infusions in total). The recommended dosage of Rixathon for the treatment of pemphigus vulgaris is 1000 mg administered as an IV infusion followed two weeks later by a second 1000 mg IV infusion in

combination with a tapering course of glucocorticoids A maintenance infusion of 500 mg IV should be administered at month 12 and then every 6 months thereafter based on clinical evaluation.

Treatment of relapse consider resuming or increasing the patient's glucocorticoid dose based on clinical evaluation. HBcAb-status. These can be complemented with other appropriate markers as per local monoclonal antibodies. Subsequent infusions may be administered no sooner than 16 weeks following the previous guidelines. Patients with active hepatitis B disease should not be treated with Rixathon.

Special populations Paediatric population The safety and efficacy of rituximab in children below 18 years has not been established. It

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

intravenous infusion through a dedicated line. It should not be administered as an intravenous push or bolus. initially resumed at not more than one-half the previous rate.

treatment should be seriously considered on a case by case basis. Mild or moderate infusion-related reactions (IRR) (section 4.8) usually respond to a reduction Mean pre-therapeutic antibody titres against a panel of antigens (Streptococcus pneumoniae, in milk (relative infant dose less than 0.4%). Few case of follow-up of breastfed infants in the rate of influsion. The influsion rate may be increased upon improvement of symptoms. The recommended initial rate for infusion is 50 mg/h; after the first 30 minutes, it can be Skin reactions

escalated in 50 mg/h increments every 30 minutes, to a maximum of 400 mg/h. subsequent infusions

Subsequent doses of Rixathon can be infused at an initial rate of 100 mg/h, and increased by 100 mg/h increments at 30 minute intervals, to a maximum of 400 mg/h

Alternative subsequent, faster, infusion schedule If patients did not experience a serious infusion related reaction with their first or subsequent infusions of a dose of 1000 mg Rixathon administered over the standard infusion schedule, a more rapid infusion can be administered for second and subsequent infusions using the same <u>Infusion related reactions</u> concentration as in previous infusions (4 mg/mL in a 250 mL volume). Initiate at a rate of Rituximab is associated with infusion related reactions (IRRs), which may be related to release 250mg/hour for the first 30 minutes and then 600 mg/hour for the next 90 minutes. If the more of cytokines and/or other chemical mediators pid infusion is tolerated, this infusion schedule can be used when administering subsequent

Severe IRRs with fatal outcome have been reported in rheumatoid arthritis patients in the

previous serious infusion reactions to any prior biologic therapy or to rituximab, should not be like headache, pruritus, throat irritation, flushing, rash, urticaria, hypertension, and pyrexia. In following induction treatment) or in combination with chemotherapy. administered the more rapid infusion.

Contraindications for use in non-Hodgkin's lymphoma and chronic lymphocytic leukaemia listed in section 6.1. Active, severe infections (see section 4.4).

previously untreated and relapsed/refractory chronic lymphocytic leukaemia. Only limited data

Contraindications for use in rheumatoid arthritis, granulomatosis with polyangiitis (GPA), mg/h to 50 mg/h) when symptoms have completely resolved. Hypersensitivity to the active substance or to murine proteins, or to any of the other excipients

4.4 Special warnings and precautions for use

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

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 professional, and in an environment where full resuscitation facilities are immediately available indicative of neurological dysfunction, and if so, whether these symptoms are possibly suggestive of PML. Consultation with a Neurologist should be considered as clinically If any doubt exists, further evaluation, including MRI scan preferably with contrast, Premedication consisting of an anti-pyretic and an antihistaminic, e.g. paracetamol and cerebrospinal fluid (CSF) testing for JC Viral DNA and repeat neurological assessments, should be considered. In patients with non-Hodgkin's lymphoma and chronic lymphocytic leukaemia, premedication The physician should be particularly alert to symptoms suggestive of PML that the patient may role in maintaining normal immune response, patients have an increased risk of infection following

advised to inform their partner or caregivers about their treatment, since they may notice symptoms that the patient is not aware of.

Non-Hodgkin's lymphoma and chronic lymphocytic leukaemia Infusion related reactions Rituximab is associated with infusion related reactions, which may be related to release of

be given on the same day as the first infusion of Rixathon). This should be followed by oral This set of reactions which includes syndrome of cytokine release, tumour lysis syndrome and Severe infusion related reactions with fatal outcome have been reported during postmarketing of rituximab. Pneumocystis jirovecii pneumonia (PJP) prophylaxis is recommended for patients with GPA/MPA use of the rituximab intravenous formulation, with an onset ranging within 30 minutes to 2 hours or PV during and following Rixathon treatment, as appropriate according to local clinical practice after starting the first rituximab intravenous infusion. They were characterized by pulmonary False negative serologic testing of infections

Severe cytokine release syndrome is characterised by severe dyspnoea, often accompanied by Hepatitis B Infections The recommended dose of Rixathon in combination with chemotherapy for induction treatment bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. This Cases of hepatitis B reactivation, including those with a fatal outcome, have been reported in hyperuricaemia, hyperkalaemia, hypercalcaemia, hyperphosphataemia, acute renal failure, elevaded lactate dehydrogenase (LDH) and may be associated with acute respiratory failure. Hepatitis B virus (HBV) screening should be performed in all patients before initiation of and death. The acute respiratory failure may be accompanied by events storing an death. The acute respiratory failure may be accompanied by events storing an death. The summarifests interstitial infiltration or oedema, visible on a chest X-ray. The syndrome frequently manifests itself within one or two hours of initiating the first infusion. Patients with a history of pulmonary insufficiency or those with pulmonary tumour infiltration may be at greater risk of poor outcome insufficiency or those with pulmonary tumour infiltration may be at greater risk of poor outcome insufficiency or those with pulmonary tumour infiltration may be at greater risk of poor outcome insufficiency or those with pulmonary tumour infiltration may be at greater risk of poor outcome insufficiency or those with pulmonary tumour infiltration may be at greater risk of poor outcome insufficiency or those with pulmonary tumour infiltration may be at greater risk of poor outcome insufficiency or those with pulmonary tumour infiltration may be at greater risk of poor outcome insufficiency or those with pulmonary tumour infiltration may be at greater risk of poor outcome insufficiency or those with pulmonary tumour infiltration may be at greater risk of poor outcome insufficiency or those with pulmonary tumour infiltration may be at greater risk of poor outcome insufficiency or those with pulmonary tumour infiltration may be at greater risk of poor outcome insufficiency or those with pulmonary tumour infiltration may be at greater risk of poor outcome insufficiency or those with pulmonary tumour infiltration may be at greater risk of poor outcome insufficiency or those with pulmonary tumour infiltration may be at greater risk of poor outcome insufficiency or those with pulmonary tumour infiltration may be at greater risk of poor outcome insufficiency or those with pulmonary tumour infiltration may be at greater risk of poor outcome insufficiency or those with pulmonary tumour infiltration may be at greater risk of poor outcome.

should be closely monitored until tumour lysis syndrome and pulmonary infiltration have been Measure blood neutrophils prior to each course of Rixathon, and regularly up to 6-months after relapsed/refractory follicular lymphoma who have responded to induction treatment is: Further treatment of patients after complete resolution of signs and symptoms has rarely Skin reactions

release syndrome, should be treated with extreme caution. These patients should be very discontinued. The recommended dose of Rixathon monotherapy used as induction treatment for adult closely monitored throughout the first infusion. Consideration should be given to the use of a closely monitored throughout the first infusion. Consideration should be given to the use of a closely monitored throughout the first infusion in these potients are a split design over two days. required. Please see cytokine release syndrome above for severe reactions.

dosage is 375 mg/m² body surface area, administered on day 1 of each chemotherapy cycle for 8 cycles after intravenous infusion of the glucocorticoid component of CHOP. Safety and efficacy of rituximab have not been established in combination with other chemotherapies in diffuse large R cell non-Hoddkin's lumphoms. antihistamines and glucocorticoids, should be available for immediate use in the event of an antihistamines and glucocorticoids, should be available for immediate use in the event of an allergic reaction during administration of rituximab. Clinical manifestations of anaphylaxis may appear similar to clinical manifestations of the cytokine release syndrome (described above) in on-live vaccinations be required whilst receiving rituximab therapy, these should be completed ppear similar to clinical manifestations of the cytokine release syndrome (described above). Reactions attributed to hypersensitivity have been reported less frequently than those with chemotherapy, standard dose reductions for the chemotherapeutic medicinal products attributed to cytokine release. Additional reactions reported in some cases were myocardial infarction, atrial fibrillation, the proportions of patients with positive antibody titers against S. pneumoniae, influenza, pulmonary oedema and acute reversible thrombocytopenia.

> to withholding anti-hypertensive medicines 12 hours prior to the Rixathon infusion. Angina pectoris, cardiac arrhythmias such as atrial flutter and fibrillation, heart failure and/or a history of cardiac disease and/or cardiotoxic chemotherapy should be monitored closely.

considering treatment of patients with neutrophils $< 1.5 \times 10^9/L$ and/or platelet counts $< 75 \times 10^9/L$ rituximab therapy. as clinical experience in this population is limited. Rituximab has been used in 21 patients who Malignancy reduced bone marrow function without inducing myelotoxicity.

Rixathon therapy.

Serious infections, including fatalities, can occur during therapy with rituximab (see section 11.5 mmol (or 263.2 mg) sodium per 50 mL vial. To be taken into consideration by patients on 4.8). Rixathon should not be administered to patients with an active, severe infection (e.g. a controlled sodium diet. tuberculosis, sepsis and opportunistic infections, see section 4.3). Physicians should exercise caution when considering the use of Rixathon 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).

Cases of hepatitis B reactivation have been reported in subjects receiving rituximab including effect of fludarabine and cyclophosphamide on the pharmacokinetics of rituximab. fulminant hepatitis with fatal outcome. The majority of these subjects were also exposed to cytotoxic chemotherapy. Limited information from one study in relapsed/refractory CLL patients

Co-administration with methotrexate had no effect on the pharmacokinetics of rituximab in suggests that rituximab treatment may also worsen the outcome of primary hepatitis B rheumatoid arthritis patients. nfections. Hepatitis B virus (HBV) screening should be performed in all patients before Patients with human anti-mouse antibody (HAMA) or anti-drug antibody (ADA) titres may have In the event of relapse, patients may receive 1000 mg IV. The healthcare provider should also initiation of treatment with Rixathon. At minimum this should include HBsAg-status and allergic or hypersensitivity reactions when treated with other diagnostic or therapeutic Patients with positive hepatitis B serology (either HBsAg or HBcAb) should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation.

during postmarketing use of rituximab in NHL and CLL (see section 4.8). The majority of DMARD following rituximab. In these patients the rate of clinically relevant infection while on patients had received rituximab in combination with chemotherapy or as part of a hematopoletic rituximab was 6.01 per 100 patient years compared to 4.97 per 100 patient years following stem cell transplant. Cases of enteroviral meningoencephalitis including fatalities have been reported following use

4.6 Fertility, pregnancy and lactation of rituximab.

False negative serologic testing of infections

Rixathon is for intravenous use. The prepared Rixathon solution should be administered as an Due to the risk of false negative serologic testing of infections, alternative diagnostic tools should be considered in case of patients presenting with symptoms indicative of rare infectious disease e.g. West Nile virus and neuroborreliosis. 4.4). Patients who develop evidence of severe reactions, especially severe dyspnoea, bronchospasm or hypoxia should have the infusion interrupted immediately. Patients with non-Hoddkin's lymphoma should then be avaluated for evidence of typoxic should have the infusion interrupted immediately. Patients with non-Hoddkin's lymphoma should then be avaluated for evidence of typoxic should have not been proposed typoxic should have the infusion interrupted immediately. Patients with non-Hoddkin's lymphoma should then be avaluated for evidence of typoxic should have not been proposed typoxic should have the infusion interrupted immediately. Patients with non-Hoddkin's lymphoma should then be avaluated for evidence of typoxic should have the infusion interrupted immediately. Patients with live virus vaccines is not recommended.

By call levels in human neonates following maternal exposure to rituximab have not been patients. non-Hodgkin's lymphoma should then be evaluated for evidence of tumour lysis syndrome Patients treated with Rixathon may receive non-live vaccinations. However with non-live studied in clinical trials. There are no adequate and well-controlled data from studies in

a glycosylated immunoglobulin with human IgG1 constant regions and murine light-chain and including appropriate laboratory tests and, for pulmonary infiltration, with a chest X-ray. In all vaccines response rates may be reduced. In a non-randomised study, patients with relapsed pregnant women, however transient B-cell depletion and lymphocytopenia have been reported heavy- chain variable region sequences. The antibody is produced by mammalian (Chinese patients, the infusion should not be restarted until complete resolution of all symptoms, and low-grade NHL who received rituximab monotherapy when compared to healthy untreated in some infants born to mothers exposed to rituximab during pregnancy. Similar effects have normalisation of laboratory values and chest X-ray findings. At this time, the infusion can be controls had a lower rate of response to vaccination with tetanus recall antigen (16% vs. 81%) been observed in animal studies (see section 5.3). For these reasons Rixathon should not be and Keyhole Limpet Haemocyanin (KLH) neoantigen (4% vs. 76% when assessed for >2-fold administered to pregnant women unless the possible benefit outweighs the potential risk. If the same severe adverse reactions occur for a second time, the decision to stop the increase in antibody titer). For CLL patients similar results are assumable considering Breast-feeding similarities between both diseases but that has not been investigated in clinical trials.

> Severe skin reactions such as Toxic Epidermal Necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome, some with fatal outcome, have been reported (see section 4.8). Fertility In case of such an event, with a suspected relationship to rituximab, treatment should be Animal studies did not reveal deleterious effects of rituximab on reproductive organs permanently discontinued Rheumatoid arthritis, granulomatosis with polyangiitis, microscopic polyangiitis and pemphigus

Methotrexate (MTX) naïve populations with rheumatoid arthritis suggest that Rixathon would have no or negligible influence on the ability to drive and use The use of Rituximab is not recommended in MTX-naïve patients since a favourable benefit risk relationship has not been established.

postmarketing setting. In rheumatoid arthritis most infusion-related events reported in clinical from patients from clinical trials and from postmarketing surveillance. These patients were Patients who have clinically significant cardiovascular disease, including arrhythmias, or trials were mild to moderate in severity. The most common symptoms were allergic reactions treated either with rituximab monotherapy (as induction treatment or maintenance treatment general, the proportion of patients experiencing any infusion reaction was higher following the first infusion than following the second infusion of any treatment course. The incidence of IRR which occurred in the majority of patients during the first infusion. The incidence of lecreased with subsequent courses (see section 4.8). The reactions reported were usually infusion- related symptoms decreases substantially with subsequent infusions and is less than reversible with a reduction in rate, or interruption, of rituximab infusion and administration of an 1% after eight doses of rituximab. Infectious events (predominantly bacterial and viral) occurred in approximately 30-55% of

and glucocorticoids if required. Closely monitor patients with pre-existing cardiac conditions

severity of the IRR and the required interventions, temporarily or permanently discontinue

ixathon. In most cases, the infusion can be resumed at a 50% reduction in rate (e.g. from 100 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 an allergic reaction during administration of Rixathon. Rixathon is indicated, in combination with metnotrexate, to reduce signs and symptoms in adult patients with moderately to severely active rheumatoid arthritis who had an inadequate disease. In patients treated with rituximab alone or in combination with chemotherapy severely active rheumatoid arthritis who had an inadequate disease. In patients treated with rituximab alone or in combination with chemotherapy severely active rheumatoid arthritis who had an inadequate disease. In patients treated with rituximab alone or in combination with chemotherapy severely active rheumatoid arthritis who had an inadequate disease. In patients treated with rituximab alone or in combination with chemotherapy severely active rheumatoid arthritis who had an inadequate disease. In patients treated with rituximab alone or in combination with chemotherapy severely active rheumatoid arthritis who had an inadequate disease. In patients treated with rituximab alone or in combination with chemotherapy severely active rheumatoid arthritis who had an inadequate disease. In patients treated with rituximab alone or in combination with chemotherapy severely active rheumatoid arthritis who had an inadequate disease. In patients treated with rituximab alone or in combination with chemotherapy severely active research and the patients are presented as a severely active rheumatoid arthritis who had an inadequate disease. In patients treated with rituximab alone or in combination with chemotherapy severely active rheumatoid arthritis who had an inadequate disease. In patients treated with rituximab alone or in combination with chemotherapy severely active rheumatoid arthritis who had an inadequate disease. In patients treated with rituximab alone or in combination with chemotherapy severely active rheumatoid arthritis who had an inadequate disease. In patients treated with rituximab alone or in combination with chemotherapy severely active rheumatoid arthritis who had an inadequate disease.

occurrence of pre-existing ischemic cardiac conditions becoming symptomatic, such as angina are summarised in Table 1. Within each frequency grouping, undesirable effects are presented pectoris, has been observed, as well as atrial fibrillation and flutter. Therefore, in patients with in order of decreasing seriousness. Frequencies are defined as very common (≥ 1/10), common a known cardiac history, and those who experienced prior cardiopulmonary adverse reactions, the risk of cardiovascular complications resulting from infusion reactions should be considered (< 1/10,000) and not known (cannot be estimated from the available data). Within each before treatment with Rixathon and patients closely monitored during administration. Since frequency grouping, undesirable effects are presented in the order of decreasing seriousness. hypotension may occur during rituximab infusion, consideration should be given to withholding

The ADRs identified only during postmarketing surveillance, and for which a frequency could anti-hypertensive medications 12 hours prior to the Rixathon infusion. Very rare cases of fatal PML have been reported following use of rituximab. Patients must be IRRs in patients with GPA, MPA and pemphigus vulgaris were consistent with those seen for monitored at regular intervals for any new or worsening neurological symptoms or signs that rheumatoid arthritis patients in clinical trials and in the postmarketing setting (see section 4.8). Table 1 Cardiac disorders Angina pectoris, cardiac arrhythmias such as atrial flutter and fibrillation, heart failure and/or

history of cardiac disease should be monitored closely (see Infusion related reactions, Based on the mechanism of action of rituximab and the knowledge that B cells play an important with glucocorticoids should be considered if Rixathon is not given in combination with not notice (e.g. cognitive, neurological or psychiatric symptoms). Patients should also be rituximab therapy (see section 5.1). Serious infections, including fatalities, can occur during

myocardial infarction have occurred in patients treated with rituximab. Therefore patients with

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°/L it is recommended to administer stabilisation or improved outcome has been seen. It remains unknown if early detection of predispose patients with recommended to administer stabilisation or improved outcome has been seen. It remains unknown if early detection of history of recurring or choracteristic stabilisation or improved outcome has been seen. It remains unknown if early detection of history of recurring or choracteristic stabilisation or improved outcome has been seen. It remains unknown if early detection of predispose patients to serious infections, e.g. or without an administration of the minimum description description of the minimum description descriptio recommended that immunoglobulin levels are determined prior to initiating treatment with Patients reporting signs and symptoms of infection following Rixathon therapy should be promptly evaluated and treated appropriately. Before giving a subsequent course of Rixathon

treatment, patients should be re-evaluated for any potential risk for infections. Very rare cases of fatal progressive multifocal leukoencephalopathy (PMI) have been reported following use of rituximab for the treatment of rheumatoid arthritis and autoimmune diseases including Systemic Lupus Erythematosus (SLE) and vasculitis. Cases of enteroviral meningoencephalitis including fatalities have been reported following use

events and in some cases included rapid tumour lysis and features of tumour lysis syndrome in Due to the risk of false negative serologic testing of infections, alternative diagnostic tools addition to fever, chills, rigors, hypotension, urticaria, angioedema and other symptoms (see should be considered in case of patients presenting with symptoms indicative of rare infectious disease e.g. West Nile virus and neuroborreliosis of previously untreated or relapsed/refractory patients with follicular lymphoma is: 375 mg/m² syndrome may be associated with some features of tumour lysis syndrome such as rheumatoid arthritis, granulomatosis with polyangiitis and microscopic polyangiitis and other

treatment with Rixathon. At minimum this should include HBsAq-status and HBcAb-statu

cessation of treatment, and upon signs or symptoms of infection (see section 4.8). Severe skin reactions such as Toxic Epidermal Necrolysis (Lyell's syndrome) and Stevens-Patients with a high tumour burden or with a high number (≥ 25 x 10⁹/L) of circulating malignant Johnson syndrome, some with fatal outcome, have been reported (see section 4.8). In case of cells such as patients with CLL, who may be at higher risk of especially severe cytokine such an event with a suspected relationship to Rixathon, treatment should be permanently

or subsequent relapse after chemotherapy is: 375 mg/m² body surface area, administered as brought up-to-date with all immunisations in agreement with current immunisation guidelines Infusion related adverse reactions of all kinds have been observed in 77% of patients treated prior to initiating Rixathon therapy. Vaccination should be completed at least 4 weeks prior to reatment with rituximab monotherapy for relapsed/refractory follicular lymphoma, the recommended dose is: 375 mg/m² body surface area, administered as an intravenous with interruption of rituximab infusion and administration of an anti-pyretic, an antihistaminic, with live virus vaccines is not recommended whilet on Rivathon. and, occasionally, oxygen, intravenous saline or bronchodilators, and glucocorticoids if or whilst peripherally B cell depleted. ixathon should be used in combination with CHOP chemotherapy. The recommended Anaphylactic and other hypersensitivity reactions have been reported following the intravenous

In the overall experience of rituximab repeat treatment over one year in rheumatoid arthritis, mumps, rubella, varicella and tetanus toxoid were generally similar to the proportions at

Concomitant/sequential use of other DMARDs in rheumatoid arthritis e concomitant use of Rixathon and anti-rheumatic 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 myocardial infarction have occurred in patients treated with rituximab. Therefore patients with DMARDs (including TNF inhibitors and other biologics) following rituximab (see section 4.5). ² see also section infection below 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 4 see also section haematologic adverse reactions below Although rituximab is not myelosuppressive in monotherapy, caution should be exercised when closely observed for signs of infection if biologic agents and/or DMARDs are used following ⁵ see also section infusion related reactions below. Rarely fatal cases reported

underwent autologous bone marrow transplantation and other risk groups with a presumable Immunomodulatory medicinal products may increase the risk of malignancy. However, available data do not suggest an increased risk of malignancy for rituximab used in autoi Regular full blood counts, including neutrophil and platelet counts, should be performed during indications beyond the malignancy risk already associated with the underlying autoimmune Excipients: This medicinal product contains 2.3 mmol (or 52.6 mg) sodium per 10 mL vial and

> 4.5 Interaction with other medicinal products and other forms of interaction 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

Very rare cases of progressive multifocal leukoencephalopathy (PML) have been reported In patients with rheumatoid arthritis, 283 patients received subsequent therapy with a biologic treatment with the biologic DMARD

> Contraception in males and females Due to the long retention time of rituximab in B cell depleted patients, women of childbearing potential should use effective contraceptive methods during and for 12 months following

Limited data on rituximah excretion into breast milk suggest very low rituximah concentration

and the long-term outcomes of breastfed infants remain unknown breastfeeding is not mended while being treated with rituximab and optimally for 6 months following rituximab

4.7 Effects on ability to drive and use machines No studies on the effects of Rixathon on the ability to drive and use machines have been performed, although the pharmacological activity and adverse reactions reported to date

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

ummary of the safety profile The overall safety profile of rituximab in non-Hodgkin's lymphoma and CLL is based on data

and glucocorticolos il required. Glosely informor padoriso man processor sections. Depending on the in patients with CLL. patients during clinical trials in patients with NHL and in 30-50% of patients during clinical trials The most frequently reported or observed serious adverse drug reactions were

• IRRs (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.)

not be estimated, are listed under "not known"

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

signs and symptoms of cranial neuropathy. Occurred at various times up to several months after completion of rituximab therapy

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

served during postmarketing surveillance

8 includes fatal cases

ADRs reported in clinical trials or during postmarketing surveillance in patients with NHL and CLL disease treated with rituximab monotherapy/maintenance or in combination with System Organ Class | Very Common Very Rare Not known

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Infections and infestations	bacterial infections, viral infections, *bronchitis	sepsis, *pneumonia, *febrile infection, *herpes zoster, *respiratory tract infection, fungal infections, infections of unknown aetiology, *acute bronchitis, *sinusitis, hepatitis B¹		serious viral infection ² Pneumocystis jirovecii	PML	enteroviral meningoencephal itis ^{2, 3}
Blood and 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, hypoaesthesia, 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 disorders ^{4, 6}	heart failure ^{4, 6}	
Vascular disorders		hypertension, orthostatic hypotension, hypotension			vasculitis (predominately cutaneous), leukocytoclastic 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		gastro-intestinal perforation ⁷	
Skin and subcutaneous tissue disorders	pruritus, rash, *alopecia	urticaria, sweating, night sweats, *skin disorder			severe bullous skin reactions, Stevens- Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome) ⁷	
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 failure4	infusion site pain			
Investigations	decreased IgG levels					

The following terms have been reported as adverse events during clinical trials, however, were Table 2 Summary of adverse reactions reported in clinical trials or during postmarketing surveillance occurring in patients with rheumatoid arthritis receiving rituximab reported at a similar or lower incidence in the rituximab arms compared to control arms: ematotoxicity, neutropenic infection, urinary tract infection, sensory disturbance, pyrexia. Signs and symptoms suggestive of an infusion-related reaction were reported in more than 50% of patients in clinical trials, and were predominantly seen during the first infusion, usually in the first one to two hours. These symptoms mainly comprised fever, chills and rigors. Other

lushing, angioedema, bronchospasm, vomiting, nausea, urticaria/rash, fatigue, headache, Blood and lymphatic system throat irritation, rhinitis, pruritus, pain, tachycardia, hypertension, hypotension, dyspnoea, dyspepsia, asthenia and features of tumour lysis syndrome. Severe infusion-related reactions uch 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 ardiac conditions such as angina pectoris or congestive heart failure or severe cardiac disorders (heart failure, myocardial infarction, atrial fibrillation), pulmonary oedema, multi-organ failure, tumour lysis syndrome, cytokine release syndrome, renal failure, and respiratory failure were reported at lower or unknown frequencies. The incidence of infusion-related symptoms decreased substantially with subsequent infusions and is <1% of patients by the eighth cycle of rituximab (containing) treatment. Description of selected adverse reactions

Rituximab induces B-cell depletion in about 70-80% of patients but was associated with decreased serum immunoglobulins only in a minority of patients. Localized candida infections as well as Herpes zoster 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 mpared 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 haematopoe stem cell transplant. Examples of these serious viral infections are infections caused by the herpes Gastrointestinal Disorders viruses (Cytomegalovirus, Varicella Zoster Virus and Herpes Simplex Virus), JC virus (progressive multifocal leukoencephalopathy (PML)), enterovirus (meningoencephalitis) and hepatitis C viru (see section 4.4). Cases of fatal PML that occurred after disease progression and retreatment have also been reported in clinical trials. Cases of hepatitis B reactivation, have been reported, the Skin and Subcutaneous Tissue majority of which were in patients receiving rituximab in combination with cytotoxic chemotherapy. In patients with relapsed/refractory CLL, the incidence of grade 3/4 hepatitis B infection (reactivation and primary infection) was 2% in R-FC vs 0% FC. Progression of Kaposi's sarcoma has been observed in rituximab-exposed patients with pre-existing Kaposi's sarcoma. These cases occurred in non-approved indications and the majority of patients were HIV positive. Musculoskeletal disorders and Haematologic adverse reactions connective tissue disorders

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 ompared to observation. The incidence of thrombocytopenia was low (<1%, grade 3/4) and was not different between treatment arms. During the treatment course in studies with rituximab in combination with chemotherapy, grade 3/4 leucopenia (R-CHOP 88% vs. CHOP 79%, R-FC 3% vs. FC 12%), neutropenia (R-CVP 24% vs. CVP 14%; R-CHOP 97% vs. CHOP 88%, R-FC 30% vs. FC 19% in previously untreated CLL), pancytopenia (R-FC 3% vs. FC 1% in previously untreated CLL) were usually reported with higher frequencies when compared to chemotherapy alone. However, the higher incidence of neutropenia in patients treated with rituximab and chemotherapy was not associated with a higher incidence of infections and infestations compared to patients treated with chemotherapy alone. Studies in previously untreated and relapsed/refractory CLL have established that in up to 25% of patients treated with R-FC Multiple courses neutropenia was prolonged (defined as neutrophil count remaining below 1x10°/L between day

Multiple courses of treatment are associated with a similar ADR profile to that observed differences reported for the incidence of anaemia. Some cases of late neutropenia occurring nore 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 least baseline level within 4 months.

repatients with the most frequently reported events being hypotension and hypertension. Cases of ade 3 or 4 arrhythmia (including ventricular and suprayentricular tachycardia) and anging pectoris ade 3 or 4 arrhythmia (including ventricular and supraventricular tachycardia) and angina pectoris orders was comparable between patients treated with rituximab and observation. Cardiac events entricular failure, myocardial ischaemia) in 3% of patients treated with rituximab compared to <1%

2-hour intravenous infusion of rituximab. Patients with a history of a serious infusion reaction n observation. In studies evaluating rituximab in combination with chemotherapy, the incidence of rade 3 and 4 cardiac arrhythmias, predominantly supraventricular arrhythmias such as tachycardia d atrial flutter/fibrillation, was higher in the R-CHOP group (14 patients, 6.9%) as compared to the Infections verall incidence of grade 3 or 4 cardiac disorders was low both in the first-line study (4% R-FC, FC) and in the relapsed/refractory study (4% R-FC, 4% FC).

ases of interstitial lung disease, some with fatal outcome have been reported.

as no difference between the treatment groups in the incidence of other thromboembolic and vasculitis. vents. 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 chemotherapy, cases of hepatitis B reactivation have been reported (see non-Hodgkin's lymphoma receiving rituximab in combination with cytotoxic chemotherapy, cases of hepatitis B reactivation have been reported (see non-Hodgkin's lymphoma receiving rituximab in combination with cytotoxic chemotherapy, cases of hepatitis B reactivation have been reported (see non-Hodgkin's lymphoma receiving rituximab in combination with cytotoxic chemotherapy, cases of hepatitis B reactivation have been reported (see non-Hodgkin's lymphoma receiving rituximab in combination with cytotoxic chemotherapy, cases of hepatitis B reactivation have been reported (see non-Hodgkin's lymphoma receiving rituximab in combination with cytotoxic chemotherapy, cases of hepatitis B reactivation have been reported (see non-Hodgkin's lymphoma receiving rituximab in combination with cytotoxic chemotherapy). vous system disorders was low both in the first-line study (4% R-FC, 4% FC) and in the apsed/refractory study (3% R-FC, 3% FC).

ases of posterior reversible encephalopathy syndrome (PRES)/reversible posterior Cardiovascular adverse reactions koencephalopathy syndrome (RPLS) have been reported. Signs and symptoms included Serious cardiac reactions were reported at a rate of 1.3 per 100 patient years in the rituximab sual disturbance, headache, seizures and altered mental status, with or without associated treated patients. The reported treated patients compared to 1.3 per 100 patient years in placebo treated patients. The reported treated patients are reported to 1.3 per 100 patient years in placebo treated patients. ses had recognised risk factors for PRES/RPLS, including the patients' underlying disease, multiple courses. pertension, immunosuppressive therapy and/or chemotherapy. strointestinal perforation in some cases leading to death has been observed in patients

uximab was administered with chemotherapy. the clinical trial evaluating rituximab maintenance treatment in relapsed/refractory follicular hypertension, immunosuppressive therapy and/or chemotherapy. mphoma, median IgG levels were below the lower limit of normal (LLN) (< 7 g/L) after Neutropenia

duction treatment in both the observation and the rituximab groups. In the observation group, but the observation and the rituximab groups. In the observation group, the duction treatment in both the observation and the rituximab groups. In the observation group, the duction treatment in both the observation and the rituximab groups. In the observation group, the duction treatment in both the observation and the rituximab groups. In the observation group, the duction treatment in both the observation and the rituximab groups. In the observation group, the duction treatment in both the observation and the rituximab groups. In the observation group, the duction treatment in both the observation and the rituximab groups. In the observation group, the duction treatment in both the observation and the rituximab groups. In the observation group, the duction treatment in both the observation group are the duction of the duction o uximab group. The proportion of patients with IgG levels below the LLN was about 60% in e rituximab group throughout the 2 year treatment period, while it decreased in the oservation group (36% after 2 years). small number of spontaneous and literature cases of hypogammaglobulinaemia have been

ng-term immunoglobulin substitution therapy. The consequences of long term B cell depletion paediatric patients are unknown Skin and subcutaneous tissue disorders oxic Epidermal Necrolysis (Lyell syndrome) and Stevens-Johnson syndrome, some with fatal fatal outcome, have been reported very rarely. utcome, have been reported very rarely.

atient subpopulations - rituximab monotherapy Elderly patients (≥ 65 years) e incidence of ADRs of all grades and grade 3/4 ADR was similar in elderly patients infections after the development of low IgG or IgM (see section 4.4). mpared to younger patients (< 65 years). nere was a higher incidence of grade 3/4 ADRs in patients with bulky disease than in patients long-term immunoglobulin substitution therapy. The consequences of long term B cell depletion

in paediatric patients are unknown. thout bulky disease (25.6% vs. 15.4%). The incidence of ADRs of any grade was similar in Experience from granulomatosis (GPA) with polyangiitis and microscopic polyangiitis (MPA) hese two groups.

ade 3/4 ADRs) Patient subpopulations - rituximab combination therapy Elderly patients (≥ 65 years) ne 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 CLI

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 postmarketing surveillance. The safety profile of rituximab in patients with moderate to 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 postmarketing experience

Experience from rheumatoid arthritis

been reported during postmarketing experience.

reflects the expected adverse reaction profile as seen in clinical trials for rituximab(see section 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 Tabulated list of adverse reactions

Adverse reactions are listed in Table 2. Frequencies are defined as very common (≥ 1/10), common

(< 1/10,000) and not known (cannot be estimated from the available data). Within each frequency

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 subsequer

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

 $(\ge 1/100 \text{ to} < 1/10)$, uncommon $(\ge 1/1.000 \text{ to} < 1/100)$, rare $(\ge 1/10.000 \text{ to} < 1/1000)$, very rare

grouping, undesirable effects are presented in order of decreasing seriousness.

Very rare PML, reactivation of | Serious viral infection infection, urinary tract gastroenteritis, tinea hepatitis B enterovira ate neutropenia³ Serum sickness Infusion4 related related reactions reactions (generalize ertension, nausea, ras General disorders and pyrexia, pruritus, urticaria, administration site conditions throat irritation, hot flush, wheezing, laryngeal vpotension, rhinitis, rigors oedema, angioneuro tachycardia, fatique, oedema, generalized oropharyngeal pain, pruritus, anaphylaxis peripheral oedema, anaphylactoid reaction) letabolism and nutrition Psychiatric disorders depression, anxiety Nervous System disorders migraine, dizziness, Cardiac disorders atrial flutter angina pectoris, heart failure. myocardial

See also section infections below. quency category derived from laboratory values collected as part of routine laboratory monitoring in clinical trials. Frequency category derived from postmarketing data.

Reactions occurring during or within 24 hours of infusion. See also infusion-related reactions below. IRRs may occur as a result of hypersensitivity and/or to the mechanism of action. ⁵ Includes observations collected as part of routine laboratory monitoring ⁶ Includes fatal cases.

Adverse reaction

Infections and infestations

Dyspepsia, diarrhoea

reflux, mouth ulceration,

ıpper abdominal pair

musculoskeletal pair

decreased IgG levels

steoarthritis, bursitis

24 and 42 after the last dose) or occurred with a late onset (defined as neutrophil count below x10°/L later than 42 days after last dose in patients with no previous prolonged neutropenia or during the first 6 months and declined thereafter. This is mostly accounted for by IRRs (most who recovered prior to day 42) following treatment with rituximab plus FC. There were no frequent during the first treatment course), RA exacerbation and infections, all of which were MedDRA System organ class more frequent in the first 6 months of treatment Description of selected adverse reactions

Infusion-related reactions

decreased IgM levels⁵

The most frequent ADRs following receipt of rituximab in clinical studies were IRRs (refer 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 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 of the first exposure to rituximab. The incidence of IRRs declined with subsequent infusions with hyperviscosity and related symptoms. The transient IgM increase usually returned to at In clinical trials fewer than 1% (17/3189) of patients experienced a serious IRR. There were no CTC Grade 4 IRRs and no deaths due to IRRs in the clinical trials. The proportion of TC Grade 3 events and of IRRs leading to withdrawal decreased by course and were rare ardiovascular reactions during clinical trials with rituximab monotherapy were reported in 18.8% from course 3 onwards. Premedication with intravenous glucocorticoid significantly ring infusion were reported. During maintenance treatment, the incidence of grade 3/4 cardiac orders was comparable between rejorted and a posturate in the posturate and in a trial designed to evaluate the safety of a more rapid rituximab infusion in patients with rheumatoid arthritis, patients with moderate-to-severe active RA who did not experience a ere reported as serious adverse events (including atrial fibrillation, myocardial infarction, left

HOP group (3 patients, 1.5%). All of these arrhythmias either occurred in the context of a rituximab The overall rate of infection reported from clinical trials was approximately 94 per 100 patient usion or we're associated with predisposing conditions such as fever, infection, acute myocardial years in rituximab treated patients. The infections were predominately mild to moderate and irction or pre-existing respiratory and cardiovascular disease. No difference between the consisted mostly of upper respiratory tract infections and urinary tract infections. The incidence CHOP and CHOP group was observed in the incidence of other grade 3 and 4 cardiac events of infections that were serious or required IV antibiotics was approximately 4 per 100 patient cluding heart failure, myocardial disease and manifestations of coronary artery disease. In CLL, 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 In the postmarketing setting, serious viral infections have been reported in RA patients treated with rituximab. rring the treatment period (induction treatment phase comprising of R-CHOP for at most Cases of progressive multifocal leukoencephalopathy with fatal outcome have been reported th cycles), four patients (2%) treated with R-CHOP, all with cardiovascular risk factors, following use of rituximab for the treatment of autoimmune diseases. This includes rheumatoic perienced thromboembolic cerebrovascular accidents during the first treatment cycle. There arthritis and off- label autoimmune diseases, including Systemic Lupus Erythematosus (SLE)

> lymphoma). Reactivation of hepatitis B infection has also been very rarely reported in RA patients receiving rituximab (see Section 4.4). proportions of patients experiencing cardiac reactions (all or serious) did not increase ove

Neurologic events Cases of posterior reversible encephalopathy syndrome (PRES) / reversible posterior leukoencephalopathy syndrome (RPLS) have been reported. Signs and symptoms included ceiving rituximab for treatment of non-Hodgkin's lymphoma. In the majority of these cases, visual disturbance, headache, seizures and altered mental status, with or without associated hypertension. A diagnosis of PRES/RPLS requires confirmation by brain imaging. The reported cases had recognised risk factors for PRES/RPLS, including the patients' underlying disease,

transient and mild or moderate in severity. Neutropenia can occur several months after the administration of rituximab (see section 4.4). In placebo-controlled periods of clinical trials, 0.94% (13/1382) of rituximab treated patients and 0.27% (2/731) of placebo patients developed severe neutropenia. served in paediatric patients treated with rituximab, in some cases severe and requiring

Neutropenic events, including severe late onset and persistent neutropenia, have been rarely reported in the postmarketing setting, some of which were associated with fatal infections. Skin and subcutaneous tissue disorders oxic Epidermal Necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome, some with

Laboratory abnormalities Hypogammaglobulinaemia (IgG or IgM below the lower limit of normal) has been observed in RA patients treated with rituximab. There was no increased rate in overall infections or serious A small number of spontaneous and literature cases of hypogammaglobulinaemia have been observed in paediatric patients treated with rituximab, in some cases severe and requiring

Induction of remission (GPA/MPA Study 1) The percentage of patients reporting ADRs upon re-treatment with further courses of rituximab In the GPA/MPA study 1, 99 patients were treated for induction of remission of GPA and MPA as similar to the percentage of patients reporting ADRs upon initial exposure (any grade and with rituximab (375 mg/m², once weekly for 4weeks) and glucocorticoids (see section 5.1). The ADRs listed in Table 3 were all adverse events which occurred at an incidence of ≥ 5% in the rituximab group and at a higher frequency than the comparator group.

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

Frequency

toxic Epiderma

(Lyell's syndrome

Stevens-Johnsor

7% 5% 5% 5% not known 7% 5% 5% 44% 10% 10% 12% 5% 12% 11% 6%
5% 5% not known not known 7% 5% 5% 14% 10% 10% 12% 5% 12% 11% 11%
5% not known not known 7% 5% 5% 14% 10% 10% 12% 5% 12% 11% 11%
not known not known 7% 5% 5% 14% 10% 10% 12% 5% 12% 11% 11%
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11%
11%
6%
18%
6%
5%
7%
18%
15%
10%
5%
5%
5%
16%
6%
ns below.

Study 2 (Rituximab n=57), and at a higher frequency than the comparator group, or during postmarketing surveillance. MedDRA System Organ Class Frequency Infections and infestations Serious viral infection not known General disorders and administration site conditions Influenza-like illness Oedema peripheral astrointestinal disorders Respiratory, thoracic and mediastinal disorders Injury, poisoning and procedural complications Infusion-related reactions² Observed during postmarketing surveillance. See also section infections below.

the rituximab arm were mild or moderate in intensity. No patients in the rituximab arm had fatal The most commonly reported events considered as ADRs were infusion-related reactions and Long-term follow-up (GPA/MPA Study 3)

drug reactions section.

In a long-term observational safety study, 97 GPA and MPA patients received treatment with rituximab (mean of 8 infusions [range 1-28]) for up to 4 years, according to their physician's standard practice and discretion. The overall safety profile was consistent with the wellestablished safety profile of rituximab in GPA and MPA and no new adverse drug reactions

Details on infusion related reactions are provided in the description of selected adverse

The overall safety profile was consistent with the well-established safety profile for rituximab in

approved autoimmune indications, including GPA and MPA. Overall, 4% of patients in the

ituximab arm experienced adverse events leading to discontinuation. Most adverse events in

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Description of selected adverse drug reactions

Infusion related reactions In GPA/MPA Study 1 (adult induction of remission study). IRRs were defined as any adverse severity of these events.

In GPA/MPA Study 2 (adult maintenance study),7/57 (12%) patients in the rituximab arm experienced at least one infusion-related reaction. The incidence of IRR symptoms was experienced at least one infusion-related reaction. The incidence of IRR symptoms was common infections in the rituximab group were upper respiratory tract infection, and unique tract infection, six patients (9%) in the

Respiratory, Thoracic and Mediastinal Disorders and Skin and Subcutaneous Tissue

In GPA/MPA Study 1, the overall rate of infection was approximately 237 per 100 patient Laboratory abnormalities years (95% CI 197 - 285) at the 6-month primary endpoint. Infections were predominately In PV Study 2, in the rituximab arm, transient decreases in lymphocyte count, driven by mild to moderate and consisted mostly of upper respiratory tract infections, herpes zoster decreases in the peripheral T-cell populations, as well as a transient decrease in The rate of serious infections was approximately 25 per 100 patient years. The most be induced by IV methylprednisolone premedication infusion. frequently reported serious infection in the rituximab group was pneumonia at a frequency In PV Study 2, low IgG levels were commonly observed and low IgM levels were very

In GPA/MPA Study 2, 30/57 (53%) patients in the rituximab arm experienced infections. infections after the development of low IgG or IgM. The incidence of all grade infections was similar between the arms. Infections were Reporting of suspected adverse reactions predominately mild to moderate. The most common infections in the rituximab arm included Reporting suspected adverse reactions after authorisation of the medicinal product is In the postmarketing setting, serious viral infections have been reported in GPA/MPA

In GPA/MPA Study 1, the incidence of malignancy in rituximab treated patients in the graulomatosis with polyangiitis and microscopic polyangiitis and microscopic

Cardiovascular adverse reactions

vears (95% CI 149 - 470) at the 6-month primary endpoint. The rate of serious cardiac of 2 g of rituximab. events was 2.1 per 100 patient years (95% CI 3 - 15). The most frequently reported events were tachycardia (4%) and atrial fibrillation (3%) (see section 4.4). Neurologic events Cases of posterior reversible encephalopathy syndrome (PRES)/reversible posterior

leukoencephalopathy syndrome (RPLS) have been reported in autoimmune conditions. Signs and symptoms included visual disturbance, headache, seizures and altered mental status with or without associated hypertension. A diagnosis of PRES/RPLS requires confirmation by brain imaging. The reported cases had recognised risk factors for PRES/RPLS, including the quality, safety and efficacy to the reference medicinal product MabThera. More detailed patients' underlying disease, hypertension, immunosuppressive therapy and/or chemotherapy. reported in GPA and MPA patients receiving rituximab in the postmarketing setting.

Hypogammaglobulinaemia maglobulinaemia (IgA, IgG or IgM below the lower limit of normal) has been observed in GPA and MPA patients treated with rituximab. In GPA/MPA Study 2, no clinically meaningful differences between the two treatment arms

In GPA/MPA Study 1, 24% of patients in the rituximab group (single course) and 23% of patients in the cyclophosphamide group developed CTC grade 3 or greater neutropenia. Neutropenia was not associated with an observed increase in serious infection in In GPA/MPA Study 2, the incidence of all-grade neutropenia was 0% for rituximab- treated patients vs 5% for azathioprine treated patients. Skin and subcutaneous tissue disorders

fatal outcome, have been reported very rarely.

Experience from pemphigus vulgaris ımmary of the safety profile in PV Study 1 (Study ML22196) and PV Study 2 (Study The safety profile of rituximab in combination with short-term, low-dose glucocorticoids in the treatment of patients with pemphigus vulgaris was studied in a Phase 3, randomised, controlled, multicenter, open-label study in pemphigus patients that included 38 pemphigus rulgaris (PV) patients randomised to the rituximab group (PV Study 1). Patients randomised Follicular lymphoma to the rituximab group received an initial 1000 mg IV on Study Day 1 and a second 1000 mg Monotherapy IV on Study Day 15. Maintenance doses of 500 mg IV were administered at months 12 and Initial treatment, weekly for 4 doses 18. Patients could receive 1000 mg IV at the time of relapse (see section 5.1). In PV Study 2, a randomized, double-blind, double-dummy, active-comparator, multicenter cell NHL received 375 mg/m² of rituximab as an intravenous infusion once weekly for four

IV on Study Day 15 repeated at Weeks 24 and 26) for up to 52 weeks (see section 5.1). The safety profile of rituximab in PV was consistent with the established safety profile in other approved autoimmune indications.

Tabulated list of adverse reactions for PV Studies 1 and 2 ≥ 5% of patients in the rituximab arm and assessed as related

1 (up to month 24) and PV Study 2 (up to Week 52), or during postmarketing factors: histological type, bcl-2 positivity at baseline, resistance to last chemotherapy and

MedDRA System Organ Class	Very Common	Common	Not known
Infections and infestations	Upper respiratory tract infection	Herpes virus infection Herpes zoster Oral herpes Conjunctivitis Nasopharyngitis Oral candidiasis Urinary tract infection	Serious viral infection ¹ . Enteroviral meningoencephalitis ¹
Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)		Skin papilloma	
Psychiatric disorders	Persistent depressive disorder	Major depression Irritability	
Nervous system disorders	Headache	Dizziness	
Cardiac disorders		Tachycardia	
Gastrointestinal disorders		Abdominal pain upper	
Skin and subcutaneous tissue disorders	Alopecia	Pruritus Urticaria Skin disorder	
Musculoskeletal, connective tissue and bone disorders		Musculoskeletal pain Arthralgia Back pain	
General disorders and administration site conditions		Fatigue Asthenia Pyrexia	
Injury, Poisoning and Procedural	Infusion-related reactions ²		

served during postmarketing surveillance. See also section infections below. ²See also section infections below

Infusion-related reactions for PV Study 1 included symptoms collected on the next scheduled visit after each infusion, and adverse events occurring on the day of or one day after the infusion. The most common infusion-related reaction symptoms/Preferred Terms for PV Study 1 included headaches, chills, high blood pressure, nausea, asthenia and pain. The most common infusion-related reaction symptoms/Preferred Terms for PV Study 2 demonstrated significant improvements in response rates as were dyspnea, erythema, hyperhidrosis, flushing/hot flush, hypotension/low blood pressure and rash/rash pruritic.

<u>Description of selected adverse reactions</u> Infusion-related reactions

In PV Study 1, infusion-related reactions were common (58%). Nearly all infusion-related reaction was 29% (11 patients), 40% (15 patients), 13% (5 patients), and 10% (4 patients) following the first, second, third, and fourth infusions, respectively. No patients were withdrawn from treatment due to infusion-related reactions. Symptoms of infusion-related reactions were similar in type and severity to those seen in RA and GPA/MPA patients. In PV Study 2, IRRs occurred primarily at the first infusion and the frequency of IRRs decreased with subsequent infusions: 17.9%, 4.5%, 3% and 3% of patients experienced IRRs at the first, second, third, and fourth infusions, respectively. In 11/15 patients who

experienced at least one IRR, the IRRs were Grade 1 or 2. In 4/15 patients, Grade ≥ 3 IRRs

were reported and led to discontinuation of rituximab treatment; three of the four patients experienced serious (life-threatening) IRRs. Serious IRRs occurred at the first (2 patients)

or second (1 patient) infusion and resolved with symptomatic treatment.

In PV Study 1, 14 (37%) in the rituximab group experienced treatment-related infections compared to 15 patients (42%) in the standard-dose prednisone group. The most common event occurring within 24 hours of an infusion and considered to be infusion-related by infections in the rituximab group were herpes simplex and zoster infections, bronchitis, urinary investigators in the safety population. Of the 99 patients treated with rituximab and 12 (12%) tract infection, fungal infection and conjunctivitis. Three patients (8%) in the rituximab group experienced at least one IRR. All IRRs were CTC Grade 1 or 2. The most common IRRs experienced a total of 5 serious infections (Pneumocystis jirovecii pneumonia, infective included cytokine release syndrome, flushing, throat irritation, and tremor. Rituximab was thrombosis, intervertebral discitis, lung infection, Staphylococcal sepsis) and one patient (3%) given in combination with intravenous glucocorticoids which may reduce the incidence and in the standard-dose prednisone group experienced a serious infection (Pneumocystis jirovecii

All IRR symptoms were mild or moderate and most of them were reported from the SOCs rituximab arm experienced serious infections. In the postmarketing setting, serious viral infections have been reported in PV patients treated with rituximab.

> phosphorus level were very commonly observed post-infusion. These were considered to commonly observed; however, there was no evidence of an increased risk of serious

upper respiratory tract infections, gastroenteritis, urinary tract infections and herpes zoster.

The incidence of serious infections was similar in both arms (approximately 12%). The product in the incidence of serious infections was similar in both arms (approximately 12%). The product in the incidence of serious infections was similar in both arms (approximately 12%). The product in the incidence of serious infections was similar in both arms (approximately 12%). The product is in the incidence of serious infections was similar in both arms (approximately 12%). The product is interesting to the incidence of serious infections was similar in both arms (approximately 12%). The product is interesting to the incidence of serious infections was similar in both arms (approximately 12%). The product is interesting to the incidence of serious infections was similar in both arms (approximately 12%). The product is interesting to the incidence of serious infections was similar in both arms (approximately 12%). The product is interesting to the incidence of serious infections was similar in both arms (approximately 12%). The product is interesting to the incidence of serious infections was similar in both arms (approximately 12%). The product is interesting to the incidence of serious infections was similar in both arms (approximately 12%). The product is interesting to the incidence of serious infections was similar in both arms (approximately 12%). The product is interesting to the incidence of the i most commonly reported serious infection in the rituximab group was mild or moderate

Any suspected adverse events should be reported to the Ministry of Health according to

OS rates – survival rates at the time of the analyses product. the National Regulation by using an online form https://sideeffects.health.gov.il 4.9 Overdose

ranulomatosis with polyangiitis and microscopic polyangiitis clinical study was 2.00 per on patient years at the study common closing date (when the final patient had completed study in patients with CLL. No additional safety signals were identified.

PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, monoclonal antibodies, ATC code: Rixathon is a biosimilar medicinal product, that has been demonstrated to be similar in information is available on the website of the Ministry of Health

CD20 is found on both normal and malignant B cells, but not on haematopoietic stem cells

http://www.health.gov.il/hozer/dr 127.pdf A small number of cases of hepatitis-B reactivation, some with fatal outcome, have been Rituximab binds specifically to the transmembrane antigen, CD20, a non-glycosylated phosphoprotein, located on pre-B and mature B lymphocytes. The antigen is expressed on Table 7 > 95% of all B cell non-Hodgkin's lymphomas.

pro-B cells, normal plasma cells or other normal tissue. This antigen does not internalise In GPA/MPA Study 1, at 6 months, in the rituximab group, 27%, 58% and 51% of patients with normal immunoglobulin levels at baseline, had low IgA, IgG and IgM levels, respectively compared to 25%, 50% and 46% in the cyclophosphamide group. The rate of overall The Fab domain of rituximab binds to the CD20 antigen on B lymphocytes and the Fc infections and serious infections was not increased after the development of low IgA, IgG domain can recruit immune effector functions to mediate B cell lysis. Possible mechanisms of effector-mediated cell lysis include complement-dependent cytotoxicity (CDC) resulti from C1g binding, and antibody-dependent cellular cytotoxicity (ADCC) mediated by one g or decreases in total immunoglobulin, IgG, IgM or IgA levels were observed throughout the more of the Fcy receptors on the surface of granulocytes, macrophages and NK cells. Rituximab binding to CD20 antigen on B lymphocytes has also been demonstrated to induce cell death via apoptosis. Peripheral B cell counts declined below normal following completion of the first dose of rituximab. In patients treated for haematological malignancies, B cell recovery began withi 6 months of treatment and generally returned to normal levels within 12 months after completion of therapy, although in some patients this may take longer (up to a median recovery time of 23 months post-induction therapy). In rheumatoid arthritis patients immediate depletion of B cells in the peripheral blood was observed following two infusions of 1000 mg rituximab separated by a 14 day interval. Peripheral blood B cell counts begin to se from week 24 and evidence for repopulation is observed in the majority of pati Toxic Epidermal Necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome, some with by week 40, whether rituximab was administered as monotherapy or in combination with methotrexate. A small proportion of patients had prolonged peripheral B cell depletion lasting 2 years or more after their last dose of rituximab. In patients with granulomatosis wit polyangiitis or microscopic polyangiitis, the number of peripheral blood B cells decreased to < 10 cells/µL after two weekly infusions of rituximab 375 mg/m², and remained at that level in most patients up to the 6 month timepoint. The majority of patients (81%) showed signs of I cell return, with counts > 10 cells/µL by month 12, increasing to 87% of patients by month 18.

In the pivotal trial, 166 patients with relapsed or chemoresistant low-grade or follicular B study evaluating the efficacy and safety of rituximab compared with mycophenolate mofetil

(AME) is positive to with model and safety of rituximab compared with mycophenolate mofetil

(CI 2/ 440/ 569/ with 2009 compared with mycophenolate mofetil) (MMF) in patients with moderate-to-severe PV requiring oral corticosteroids, 67 PV patients (Cl_{ss}% 41% - 56%) with a 6% complete response (CR) and a 42% partial response (PF received treatment with rituring h (initial 1000 mg N/co Strain David and 1000 mg N/co Strain David (MMP) in patients with moderate-to-severe PV requiring of at controsteroids, 67 PV patients received treatment with rituximab (initial 1000 mg IV on Study Day 1 and a second 1000 mg IV on Study Day 15 repeated at Weeks 24 and 26) for up to 52 weeks (see section 5.1).

Take: The projected median time to progression (TTP) for responding patients was 13.0 months. In a subgroup analysis, the ORR was higher in patients with IWF B, C, and D histological 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 treatment; TNLT: time to next anti lymphoma treatment. Adverse reactions from PV Studies 1 and 2 are presented in Table 5. In PV Study 1, ADRs treated with autologous bone marrow transplant (ABMT) was 78% versus 43% in patients Rituximab maintenance treatment provided consistent benefit in all predefined subgroups patients with bone marrow involvement responded compared to 59% of patients with no sample sizes were small. bone marrow involvement (p=0.0186). This finding was not supported by a stepwise Relapsed/Refractory follicular lymphoma logistic regression analysis in which the following factors were identified as prognostic

> bulky disease. eight doses. The ORR was 57% (95% Confidence interval (CI); 41% – 73%; CR 14%, PR to rituximab maintenance therapy (n=167) or observation (n=167). Rituximab maintenance 43%) with a projected median TTP for responding patients of 19.4 months (range 5.3 to treatment consisted of a single infusion of rituximab at 375 mg/m² body surface area given

> Initial treatment, bulky disease, weekly for 4 doses In pooled data from three trials, 39 patients with relapsed or chemoresistant, bulky disease a median observation time of 31 months for patients randomised to the induction phase, (single lesion ≥ 10 cm in diameter). low grade or follicular B cell NHL received 375 mg/m² R-CHOP significantly improved the outcome of patients with relapsed/refractory follicular of rituximab as intravenous infusion weekly for four doses. The ORR was 36% (CI₉₅% 21% lymphoma when compared to CHOP (see Table 8). - 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 trial, 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/m² 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% (Cl₉₅% 26% - 51%; 10% CR, 28% PR) with a projected median TTP for responding patients of 17.8 months (range 5.4 – 26.6). This compares favourably with the TTP achieved after the prior course of rituximab (12.4 months).

Initial treatment, in combination with chemotherapy In an open-label randomised trial, a total of 322 previously untreated patients with follicular partial response lymphoma were randomised to receive either CVP chemotherapy (cyclophosphamide 750 mg/m², vincristine 1.4 mg/m² up to a maximum of 2 mg on day 1, and prednisolone 40 mg/ n²/day on days 1-5) every 3 weeks for 8 cycles or rituximab 375 mg/m² in combination with 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 a cox regression analysis, the risk of experiencing progressive disease or death was a cox regression analysis, the risk of experiencing progressive disease or death was a cox regression analysis. endpoint, time to treatment failure (27 months vs. 6.6 months, p < 0.0001, log-rank test).

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). mpared to CVP, 33.6 months and 14.7 months, respectively (p = 0.0001, 109 Nation 14.7) (p=0.0039 log-rank test). In median duration of response was 37.7 months in the R-CVP group and was 13.5 (p=0.0039 log-rank test). In the R-CVP group and was 13.5 (p=0.0039 log-rank test). In the R-CVP group and was 13.5 (p=0.0039 log-rank test). In the R-CVP group and was 13.5 (p=0.0039 log-rank test). In the R-CVP group and was 13.5 (p=0.0039 log-rank test). In the R-CVP group and was 13.5 (p=0.0039 log-rank test). In the R-CVP group and was 13.5 (p=0.0039 log-rank test). In the R-CVP group and was 13.5 (p=0.0039 log-rank test). In the R-CVP group and was 13.5 (p=0.0039 log-rank test). In the R-CVP group and was 13.5 (p=0.0039 log-rank test). In the R-CVP group and was 13.5 (p=0.0039 log-rank test). In the R-CVP group and was 13.5 (p=0.0039 log-rank test). In the R-CVP group and was 13.5 (p=0.0039 log-rank test). In the R-CVP group and was 13.5 (p=0.0039 log-rank test). In the R-CVP group and was 13.5 (p=0.0039 log-rank test). In the R-CVP group and was 13.5 (p=0.0039 log-rank test). In the R-CVP group and was 13.5 (p=0.0039 log-rank test). In the R-CVP group and was 13.5 (p=0.0039 log-rank test). In the R-CVP group and was 13.5 (p=0.0039 log-rank test). In the R-CVP group and was 13.5 (p=0.0039 log-rank test). months in the CVP group (p < 0.0001, log-rank test).

nificant clinical difference (p=0.029, log-rank test stratified by centre): survival rates at 3 months were 80.9% for patients in the R-CVP group compared to 71.1% for patients in Results from three other randomised trials using rituximab in combination with chemotherapy regimen other than CVP (CHOP, MCP, CHVP/Interferon-α) have also well as in overall survival. Key results from all four studies are summarized in table 6.

tudy	Treatment, N	Median FU, months	ORR, %	CR, %	Median TTF/PFS/ EFS mo	OS rates, %
				ĺ	Median TTP:	53-months
39021	CVP, 159 R-CVP, 162	53	57 81	10 41	14.7 33.6	71.1 80.9
					P < 0.0001	p = 0.029
LSG'00	CHOP, 205 R-CHOP, 223	18	90 96	17 20	Median TTF: 2.6 years Not reached	18-months 90 95
					P < 0.001	p = 0.016
SHO-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
_2000	CHVP-IFN, 183 R-CHVP- IFN, 175	42	85 94	49 76	Median EFS: 36 Not reached	42-months 84 91
	I			l	D < 0.0001	0 000

EFS – Event Free Survival

TTF - Time to Treatment Failure

eviously untreated follicular lymphoma A total of 1078 patients responded to induction therapy, of which 1018 were randomised to The patient years at the study common the final patient had completed the follow-up period). On the basis of standardized incidence ratios, the incidence of malignancies appears to be similar to that previously reported in patients.

In the postmarketing setting five associated vasculities.

In the postmarketing setting five associat In the postmarketing setting five cases of rituximab overdose have been reported. Three surface area given every 2 months until disease progression or for a maximum period of

cases had no reported adverse event. The two adverse events that were reported were two years. previously untreated follicular lymphoma (Table 7).

analysis (Table 7)

Overview of efficacy results for rituximab maintenance vs. observation at the

	Primary analysis (median FU: 25 months)		Final analysis (median FU: 9.0 years)		
	Observation N=513		Observation N=513		
Primary efficacy Progression-free survival (median)	NR	NR	4.06 years	10.49 years	
riogression-rice survival (median) log-rank p value hazard ratio (95% CI) risk reduction	< 0.00 0.50 (0.39 50%	001 9, 0.64)	< 0.0 0.61 (0.5 39	001 2, 0.73)	
Secondary efficacy Overall survival (median)	NR	NR	NR	NR	
log-rank p value hazard ratio (95% CI) risk reduction	0.72 0.89 (0.45 119	5, 1.74)	0.79 1.04 (0.7 -6%	7, 1.40)	
Event-free survival (median) log-rank p value hazard ratio (95% CI) risk reduction	38 months < 0.00 0.54 (0.43 469	3, 0.69)	4.04 years < 0.0 0.64 (0.5	001 4, 0.76)	
TNLT (median) log-rank p value hazard ratio (95% CI) risk reduction	NR 0.000 0.61 (0.46 39%	5, 0.80)	6.11 years < 0.0 0.66 (0.5	5, 0.78)	
TNCT (median) log-rank p value hazard ratio (95% CI) risk reduction	NR 0.00 0.60 (0.44 40%	1, 0.82)	9.32 years 0.00 0.71 (0.5	9, 0.86)	
Overall response rate* chi-squared test p value odds ratio (95% CI)	55% < 0.00 2.33 (1.73		61% < 0.0 2.43 (1.8		
Complete response (CR/CRu) rate* chi-squared test p value	48%	67%	53%	67%	
orn oquarou toot p value	2.21 (1.65		2.34 (1.8		

In a prospective, open label, international, multi-centre, phase III trial, 465 patients with elapsed/refractory follicular lymphoma were randomised in a first step to induction therapy with either CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone; n=231) o In a multi-centre, single-arm trial, 37 patients with relapsed or chemoresistant, low grade or regard to baseline characteristics and disease status. A total of 334 patients achieving a follicular B cell NHL received 375 mg/m² of rituximab as intravenous infusion weekly for complete or partial remission following induction therapy were randomised in a second ster

median observation time)

"response" was the trend test of CR versus PR versus non-response (p < 0.0001)

Abbreviations: NA, not available; ORR: overall response rate; CR: complete response; PR: For patients randomised to the maintenance phase of the trial, the median observation time rituximab with any chemotherapy. (time from maintenance randomisation to relapse, disease progression or death) when Paediatric population in the rituximab maintenance arm compared to 14.3 months in the observation arm. Using endpoint, time to treatment failure (27 months vs. 6.6 months, p < 0.0001, log-rank test).

The proportion of patients with a tumour response (CR, CRu, PR) was significantly higher (p < 0.0001 Chi-Square test) in the R-CVP group (80.9%) than the CVP group (80.9%) than the rituximab maintenance group vs. 57% in the observation group. An analysis of pivotal randomised, controlled, double-blind, multicenter trial (Trial 1). overall survival confirmed the significant benefit of rituximab maintenance over observation Trial 1 evaluated 517 patients that had experienced an inadequate response or intolerance (p=0.0039 log-rank test). Rituximab maintenance treatment reduced the risk of death by to one or more TNF inhibitor therapies. Eligible patients had active rheumatoid arthritis,

(28 months median observation time)

up is required to confirm this observation.

clophosphamide 750 mg/m², doxorubicin 50 mg/m², vincristine 1.4 mg/m² up to a

had a median follow-up duration of approximately 31 months. The two treatment groups were well balanced in baseline disease characteristics and disease status. The final statistically significant improvement in the duration of event-free survival (the primary reduction in disease activity score (DAS28) than patients treated with methotrexate alone efficacy parameter; where events were death, relapse or progression of lymphoma, or (Table 11). Similarly, a good to moderate European League Against Rheumatism (EULAR) institution of a new anti-lymphoma treatment) (p=0.0001). Kaplan Meier estimates of the response was achieved by significantly more rituximab treated with The primary outcome measure was achievement of complete remission at 6 months defined 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.

12).

Radiographic response A subsequent analysis of the duration of overall survival, carried out with a median followStructural joint damage was assessed radiographically and expressed as change in remission (CR) at 6 months (Table 16). (p=0.0071), representing a risk reduction of 32%.

In GPA/MPA Study 1, cardiac events occurred at a rate of approximately 273 per 100 patient flu-like symptoms, with a dose of 1.8 g of rituximab and fatal respiratory failure, with a dose

The pre-specified primary analysis was conducted at a median observation time of 25

Of 67 patients evaluated for human anti-mouse antibody (HAMA), no responses were months from randomization, maintenance therapy with rituximab resulted in a clinically noted. Of 356 patients evaluated for HACA, 1.1% (4 patients) were positive. relevant and statistically significant improvement in the primary endpoint of investigator

Chronic lymphocytic leukaemia

protocol defined primary analysis and after 9 years median follow-up (final

	Primary analysis (median FU: 25 months)		Final analysis (median FU: 9.0 years)	
	Observation N=513	rituximab N=505	Observation N=513	
Primary efficacy Progression-free survival (median)	NR	NR	4.06 years	10.49 years
log-rank p value hazard ratio (95% CI) risk reduction	< 0.00 0.50 (0.39 50%	9, 0.64)	< 0.00 0.61 (0.53 399	2, 0.73)
Secondary efficacy Overall survival (median) log-rank p value hazard ratio (95% CI) risk reduction	NR 0.724 0.89 (0.45	5, 1.74)	NR 0.79 1.04 (0.7	7, 1.40)
Event-free survival (median) log-rank p value hazard ratio (95% CI) risk reduction	38 months < 0.00 0.54 (0.43 46%	3, 0.69)	4.04 years < 0.00 0.64 (0.54	4, 0.76)
TNLT (median) log-rank p value hazard ratio (95% CI) risk reduction	NR 0.000 0.61 (0.46 39%	5, 0.80)	6.11 years < 0.00 0.66 (0.55 349	5, 0.78)
TNCT (median) log-rank p value hazard ratio (95% CI) risk reduction	NR 0.00 0.60 (0.44 40%	1, 0.82)	9.32 years 0.00 0.71 (0.59	9, 0.86)
Overall response rate* chi-squared test p value odds ratio (95% CI)	55% < 0.00 2.33 (1.73		61% < 0.00 2.43 (1.84	
Complete response (CR/CRu) rate* chi-squared test p value odds ratio (95% CI)	48%	67%	53% < 0.00 2.34 (1.80	67% 001

due to ADRs in Study 1. In PV Study 2, ADRs were defined as adverse events occurring in correlation was noted between response rates and bone marrow involvement. 40% of treatment showed a less pronounced effect in elderly patients (> 70 years of age), however survival was reported in the R-FC compared to the FC arm. rituximab plus CHOP (R-CHOP, n=234). The two treatment groups were well balanced with

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

Table 8 Induction phase: overview of efficacy results for CHOP vs. R-CHOP (31 months

	СНОР	R-CHOP	p-value	Risk Redu
Primary Efficacy	74% 16% 58%	87% 29% 58%	0.0003 0.0005 0.9449	Na Na Na
Estimates were control Last tumour resp			or. The "prima	ry" statistica

compared to observation alone (p < 0.0001 log-rank test). The median PFS was 42.2 months compared to observation alone (p < 0.0001 log-rank test). The median PFS was 42.2 months are the compared to observation alone (p < 0.0001 log-rank test). The median PFS was 42.2 months are the compared to observation alone (p < 0.0001 log-rank test). The median PFS was 42.2 months are the compared to observation alone (p < 0.0001 log-rank test). The median PFS was 42.2 months are the compared to observation alone (p < 0.0001 log-rank test). The median PFS was 42.2 months are the compared to observation alone (p < 0.0001 log-rank test). The median PFS was 42.2 months are the compared to observation alone (p < 0.0001 log-rank test). The compared to observation alone (p < 0.0001 log-rank test) are the compared to observation alone (p < 0.0001 log-rank test). The compared to observation alone (p < 0.0001 log-rank test) are the compared to observation alone (p < 0.0001 log-rank test). The compared to observation alone (p < 0.0001 log-rank test) are the compared to observation alone (p < 0.0001 log-rank test) are the compared to observation alone (p < 0.0001 log-rank test) are the compared to observation alone (p < 0.0001 log-rank test) are the compared to observation alone (p < 0.0001 log-rank test) are the compared to observation alone (p < 0.0001 log-rank test) are the compared to observation alone (p < 0.0001 log-rank test) are the compared test are the compared t

Efficacy Parameter	Kaplan-Meio Time to	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	20.1	38.8	<0.0001	50%
treatment				
Disease-free survivala	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%

The benefit of rituximab maintenance treatment was confirmed in all subgroups analysed, Clinically and statistically significant improvement was also noted on all individual Clinical laboratory findings regardless of induction regimen (CHOP or R-CHOP) or quality of response to induction components of the ACR response (tender and swollen joint counts, patient and physician A total of 392/3095 (12.7%) patients with rheumatoid arthritis tested positive for ADA in treatment (CR or PR) (table 9). Rituximab maintenance treatment significantly prolonged median PFS in patients responding to CHOP induction therapy (median PFS 37.5 months s. 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-

Adult 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 maximum of 2 mg on day 1, and prednisolone 40 mg/m²/day on days 1-5) every 3 weeks for eight cycles, or rituximab 375 mg/m² plus CHOP (R-CHOP). Rituximab was administered on the first day of the treatment cycle. The final efficacy analysis included all randomised patients (197 CHOP, 202 R-CHOP), and

Clinical laboratory findings

assessed progression-free survival (PFS) as compared to observation in patients with In two open-label randomised trials, a total of 817 previously untreated patients and 552 patients with relapsed/refractory CLL were randomised to receive either FC chemotherapy Significant benefit from maintenance treatment with rituximab was also seen for the (fludarabine 25 mg/m², cyclophosphamide 250 mg/m², days 1-3) every 4 weeks for 6 cycles or condary endpoints event-free survival (EFS), time to next anti-lymphoma treatment rituximab in combination with FC (R-FC). Rituximab was administered at a dosage of 375 mg/ TNLT) time to next chemotherapy (TNCT) and overall response rate (ORR) in the primary m² during the first cycle one day prior to chemotherapy and at a dosage of 500 mg/m² on day 1 of each subsequent treatment cycle. Patients were excluded from the study in relansed/ Data from extended follow-up of patients in the study (median follow-up 9 years) confirmed refractory CLL if they had previously been treated with monoclonal antibodies or if they were the long- term benefit of rituximab maintenance therapy in terms of PFS, EFS, TNLT and 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 (Table 10a and Table 10b) and 552 patients (276 R-FC, 276 FC) for the relapsed/refractory of RTX + MTX by one year

tudy (Table 11) were analysed for efficacy. In the first-line study, after a median observation time of 48.1 months, the median PFS was Inhibition of the rate of progressive joint damage was also observed long term. Radiographic 5 months in the R-FC group and 33 months in the FC group (p < 0.0001, log-rank test). analysis at 2 years in Trial 1 demonstrated significantly reduced progression of structural Relapsing The analysis of overall survival showed a significant benefit of R-FC treatment over FC chemotherapy alone (p=0.0319, log- rank test) (Table 10a). The benefit in terms of PFS methotrexate alone as well as a significantly higher proportion of patients with no was consistently observed in most patient subgroups analysed according to disease risk at progression of joint damage over the 2 year period paseline (i.e. Binet stages A-C) (Table 10b)

Efficacy Parameter	Kaplan-Meie	Risk Reduction		
	FC (N=409)	R-FC (N=408)	Log-Rank p value	
Progression-free survival (PFS)	32.8	55.3	<0.0001	45%
Overall Survival	NR	NR	0.0319	27%
Event Free Survival	31.3	51.8	<0.0001	44%
Response rate (CR, nPR, or PR) CR rates	72.6% 16.9%	85.8% 36.0%	<0.0001 <0.0001	n.a. n.a.
Duration of response*	36.2	57.3	<0.0001	44%
Disease free survival (DFS)**	48.9	60.3	0.0520	31%
Time to new treatment	47.2	69.7	<0.0001	42%

Table 10b First-line treatment of chronic lymphocytic leukaemia Hazard ratios of progression-free survival according to Binet stage (ITT) - 48.1

Progression-free survival (PFS)		ber of ents	Hazard Ratio (95% CI)	p-value (Wald test,
	FC	R-FC		not adjusted)
Binet stage A	22	18	0.39 (0.15; 0.98)	0.0442
Binet stage B	259	263	0.52 (0.41; 0.66)	<0.0001
Binet stage C	126	126	0.68 (0.49; 0.95)	0.0224
CI: Confidence Interval				

Were defined as adverse events which occurred at a rate of ≥ 5% among rituximab-treated with no ABMT. Neither age, sex, lymphoma grade, initial diagnosis, presence or absence or absence of disease flares, and change in health-related quality of life, as measured was 30.6 months in the FC group (p=0.0002, log-rank the total number of disease flares, and change in health-related quality of life, as measured to severe the total number of disease flares, and change in health-related quality of life, as measured the total number of disease flares, and change in health-related quality of life, as measured to severe the total number of disease flares, and change in health-related quality of life, as measured the total number of disease flares, and change in health-related quality of life, as measured the total number of disease flares, and change in health-related quality of life, as measured the total number of disease flares, and change in health-related quality of life, as measured the total number of disease flares, and change in health-related quality of life, as measured the total number of disease flares, and change in health-related quality of life, as measured the total number of disease flares, and change in health-related quality of life, as measured the total number of disease flares, and change in health-related quality of life, as measured the total number of disease flares, and change in health-related quality of life, as measured the total number of disease flares, and change in health-related quality of life, as measured the total number of disease flares, and change in health-related quality of life, as measured the total number of disease flares, and change in health-related quality of life. were defined as adverse events which occurred at a rate of 25% affilioning fluximab-treated of bulky disease, normal or high LDH nor presence of extranodal disease had a statistically of achieving ACR70. At week 48 seropositive patients were 2-3 orally at a dose of 2 mg/kg/day for 12 months, then 1.5 mg/kg/day for 12 months, and finally of the statistically of achieving ACR70. At week 48 seropositive patients were 2-3 orally at a dose of 2 mg/kg/day for 12 months, and finally of the statistically significant results of the control of the c group and the standard-dose prednisone group up to month 24. No patients were withdrawn significant improvement in overall times more likely to achieve ACR responses compared to seronegative patients. Seropositive 1 mg/kg/day for 4 months (treatment discontinuation after these 22 months)). Prednisone of the benefit of maintenance according to disease risk at baseline. A slight but not significant improvement in overall times more likely to achieve ACR responses compared to seronegative patients. Seropositive 1 mg/kg/day for 4 months (treatment discontinuation after these 22 months)). Prednisone of the benefit of maintenance according to disease risk at baseline. A slight but not significant induction treatment (CR,CRu or PR). Exploratory analyses of the benefit of maintenance according to disease risk at baseline. A slight but not significant improvement in overall times more likely to achieve ACR responses compared to seronegative patients. Seropositive of maintenance according to disease risk at baseline. A slight but not significant improvement in overall times more likely to achieve ACR responses compared to seronegative patients. Seropositive of maintenance according to disease risk at baseline. A slight but not significant improvement in overall times more likely to achieve ACR responses compared to seronegative patients. Seropositive of maintenance according to disease risk at baseline. A slight but not significant improvement in overall times more likely to achieve ACR responses compared to seronegative patients. Seropositive of maintenance according to disease risk at baseline. A slight but not significant improvement in overall times more likely to achieve ACR responses compared to seronegative patients. Seropositive of the benefit of maintenance according to the seronegative patients are seronegative patients. Seropositive of the benefit of maintenance according to the benefit of maintenance according to the seronegative patients. Seropositive of the benefit of maintenance according to the seronegati

Table 11 Treatment of relapsed/refractory chronic lymphocytic leukaemia - overview of patients (Figure 1). efficacy results for rituximab plus FC vs. FC alone (25.3 months median

Efficacy Parameter	Kaplan-M Time	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 * Disease free survival (DFS)** Time to new CLL treatment	27.6 42.2 34.2	39.6 39.6 NR	0.0252 0.8842 0.0024	31% -6% 35%

only applicable to patients achieving a CR, nPR, PR; NR: not reached n.a.: not applicable *: only applicable to patients achieving a CR;

Results from other supportive studies using rituximab in combination with other cal test for chemotherapy regimens (including CHOP, FCM, PC, PCM, bendamustine and cladribine) for the treatment of previously untreated and/or relapsed/refractory CLL patients have also demonstrated high overall response rates with benefit in terms of PFS rates, albeit with modestly higher toxicity (especially myelotoxicity). These studies support the use of was 28 months from maintenance randomisation. Maintenance treatment with rituximab led to a clinically relevant and statistically significant improvement in the primary endpoint, PFS,

liagnosed according to the criteria of the American College of Rheumatology (ACR) The difference between the treatment groups with respect to overall survival showed a Patients received 2 x 1000 mg intravenous infusions of rituximab or placebo in combination with MTX. All patients received concomitant 60 mg oral prednisone on days 2-7 and 30 mg on days 8-14 following the first infusion. The primary endpoint was the proportion of patients who achieved an ACR20 response at week 24. Patients were followed beyond

Figure 2: ACR responses for 4 treatment courses (24 weeks after each course (within week 24 for long term endpoints, including radiographic assessment at 56 weeks and at 104 weeks. During this time, 81% of patients, from the original placebo group received rituximab between weeks 24 and 56, under an open label extension study protocol. Trials of rituximab in patients with early arthritis (patients without prior methotrexate treatment and patients with an inadequate response to methotrexate, but not yet treated with TNF-alpha inhibitors) have met their primary endpoints. Rituximab is not indicated for these patients, since the safety data about long-term rituximab treatment are insufficient, in Disease activity outcomes

particular concerning the risk of development of malignancies and PML Rituximab in combination with methotrexate significantly increased the proportion of patients achieving at least a 20% improvement in ACR score compared with patients treated with methotrexate alone (Table 12). Across all development studies the treatment benefit was similar in patients independent of age, gender, body surface area, race, number of prior treatments or disease status.

2	Clinical response outcomes at primary endpoint in Trial 1(ITT population)				
	Outcome [†]	Placebo+MTX	rituximab+MTX (2 x 1000 mg)		
		N = 201	N = 298		
	ACR20 ACR50 ACR70	36 (18%) 11 (5%) 3 (1%)	153 (51%)*** 80 (27%)*** 37 (12%)***		
	EULAR Response (Good/Moderate)	44 (22%)	193 (65%)***		
	Mean Change in DAS	-0.34	-1.83***		

efficacy analys

Newly diagnosed

Worst case imputation is applied for patients with missing data

Complete Remission at 12 and 18 months

efficacy in the induction of remission trial.

Adult Maintenance treatment

in the azathioprine group (14%).

Number of Subjects with Major Relapse

Clinical experience in pemphigus vulgaris

safety or efficacy in the maintenance therapy clinical trial.

Laboratory evaluations

PV Study 1 (Study ML22196)

defined by Harman's criteria.

up duration of 60 months, confirmed the benefit of R-CHOP over CHOP treatment modified Total Sharp Score (mTSS) and its components, the erosion score and joint space Efficacy was observed both for patients with newly diagnosed disease and for patients with narrowing score. he analysis of all secondary parameters (response rates, progression-free survival, In Trial 1, conducted in patients with inadequate response or intolerance to one or more TNF 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 significantly less radiographic progression than patients originally receiving methotrexate (Intent-to-Treat Population*) rituximab either as rescue between weeks 16-24 or in the extension trial, before week 56, A

Outcome at 24 week

2.30 1.32	(n = 273) 1.01* 0.60*
1.32	0.60*
0.98	0.41**
46%	53%, NS
52%	60%, NS

* p < 0.05, ** p < 0.001. Abbreviation: NS, non significant Physical function and quality of life outcomes

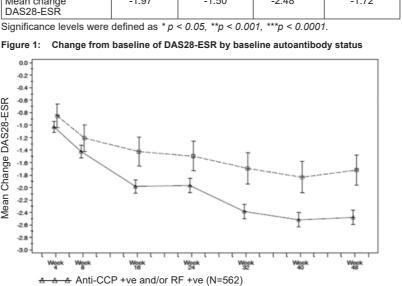
In the rituximab group, 48% of patients achieved CR at 12 months, and 39% of patients rignificant reductions in disability index (HAQ-DI) and fatigue (FACIT-Fatigue) scores were azathioprine for maintenance of complete remission), 39% of patients achieved CR at bserved in patients treated with rituximab compared to patients treated with methotrexate 12 months, and 33% of patients achieved CR at 18 months. From month 12 to month 18, 8 Index, PDAI, activity score of ≥ 15). alone. The proportions of rituximab treated patients showing a minimal clinically important relapses were observed in the rituximab group compared with four in the cyclophosphamide of B cells in the lymphoid organs of the foetuses was observed, which persisted post one hundred and thirty-five patients were randomized to treatment with rituximab group compared with four in the cyclophosphamide of B cells in the lymphoid organs of the foetuses was observed, which persisted post one hundred and thirty-five patients were randomized to treatment with rituximab group compared by a degree of 2020 was not always accompanied by a degree ifference (MCID) in HAQ-DI (defined as an individual total score decrease of >0.22) was group. also higher than among patients receiving methotrexate alone (Table 14). Retreatment with rituximab Significant improvement in health related quality of life was also demonstrated with Based upon investigator judgment, 15 patients received a second course of rituximab by Week 24. ficant improvement in both the physical health score (PHS) and mental health score in the physical health score (PHS) and mental health score the physical health score in both the physical health score in both

for these scores (Table 14).		•				
Table 14 Physical function and quality of life outcomes at week 24 in Trial 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 % SF-36 PHS MCID Mean Change in SF-36 MHS % SF-36 MHS MCID	0.9 13% 1.3 20%	5.8*** 48%*** 4.7** 38%*				

Significant difference from placebo at the primary time point: * p < 0.05, **p < 0.001 rituximab (58 patients) in a prospective, multi-center, controlled, open-label study. Included (response rate [%]) patients were 21 to 75 years of age and had newly diagnosed or relapsing disease in * p ≤ 0.0001 MCID HAQ-DI ≥ 0.22, MCID SF-36 PHS > 5.42, MCID SF-36 MHS > 6.33 complete remission after combined treatment with glucocorticoids and pulse Efficacy in autoantibody (RF and or anti-CCP) seropositive patients cyclophosphamide. The majority of patients were ANCA-positive at diagnosis or during the Patients seropositive to Rheumatoid Factor (RF) and/or anti- Cyclic Citrullinated Peptide course of their disease; had histologically confirmed necrotizing small-vessel vasculitis (anti-CCP) who were treated with rituximab in combination with methotrexate showed an with a clinical phenotype of GPA/MPA, or renal limited ANCA-associated vasculitis; or both. Remission-induction therapy included IV prednisone, administered as per the investigator's Efficacy outcomes in rituximab treated patients were analysed based on autoantibody status discretion, preceded in some patients by methylprednisolone pulses, and pulse ior to commencing treatment. At Week 24, patients who were seropositive to RF and/or anti-CCP at baseline had a significantly increased probability of achieving ACR20 and 50 maximum of 1 month after the last cyclophosphamide pulse, patients were randomly assigned esponses compared to seronegative patients (p=0.0312 and p=0.0096) (Table 15). These to receive either rituximab (two 500 mg IV infusions separated by two weeks (on Day 1 and The analysis of all secondary parameters (including cumulative oral corticosteroid dose,

patients also had a significantly greater decrease in DAS28-ESR compared to seronegative treatment was tapered and then kept at a low dose (approximately 5 mg per day) for at least

	We	ek 24	Week 48			
	Seropositive (n=514)	Seronegative (n=106)	Seropositive (n=506)	Seronegative (n=101)		
ACR20 (%)	62.3*	50.9	71. 1*	51.5		
ACR50 (%)	32.7*	19.8	44.9**	22.8		
ACR70 (%)	12.1	5.7	20.9*	6.9		
EULAR Response (%)	74.8*	62.9	84.3*	72.3		
Mean change DAS28-ESR	-1.97**	-1.50	-2.48***	-1.72		



B-B- Anti-CCP -ve and/or RF -ve (N=116) ong-term efficacy with multiple course therapy ment with rituximab in combination with methotrexate over multiple courses resulted

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. patient, within visit) in patients with an inadequate response to TNF-inhibitors Note: Patients were censored at month 28 if they had no event.

ACR20 I

■ ACR50 ACR70

clinical studies following therapy with rituximab. The emergence of ADA was not associated vith clinical deterioration or with an increased risk of reactions to subsequent infusions in or allergic reactions after the second infusion of subsequent courses. Paediatric population See Section 4.2 for information on paediatric use.

linical Experience in granulomatosis with polyangiitis (Wegener's) and microscopic therapy for two months or more (CRoff for ≥ 2 months). Adult Induction of remission GPA/MPA Study, a total of 197 patients aged 15 years or older with severely, active

anulomatosis with polyangiitis (75%) and microscopic polyangiitis (24%) were enrolled and (see Table 18). ed in an active-comparator, randomised, double-blind, multicenter, non-inferiority trial. Patients were randomised in a 1:1 ratio to receive either oral cyclophosphamide daily 2 mg/kg/day) for 3-6 months or rituximab (375 mg/m²) once weekly for 4 weeks. All patients Table 18 Percentage of PV patients who achieved complete remission off corticosteroid therapy for two months or more at month 24 (Intent-to-Treat Population - PV) phosphamide arm received azathioprine maintenance therapy in during follow-up. Patients in both arms received 1000 mg of pulse intravenous (IV) methylprednisolone (or analysis confirmed that R-CHOP treatment was associated with a clinically relevant and Patients treated with rituximab in combination with methotrexate had a significantly greater another equivalent-dose glucocorticoid) per day for 1 to 3 days, followed by oral prednisone mg/kg/day, not exceeding 80 mg/day). Prednisone tapering was to be completed by 6 months from the start of trial treatment.

median duration of event-free survival were 35 months in the R-CHOP arm compared to 13 rituximab and methotrexate alone (Table as a Birmingham Vasculitis Activity Score for Wegener's granulomatosis (BVAS/WG) of 0, and (response rate [%]) a p-value is from Fisher's exact test with mid-p correction off glucocorticoid therapy. The prespecified non-inferiority margin for the treatment difference was 20%. The trial demonstrated non-inferiority of rituximab to cyclophosphamide for complete b 95% confidence interval is corrected Newcombe interval. The number of rituximab plus low-dose prednisone patients off prednisone therapy or on relapsing disease (Table 17). ituximab (Figure 4).

Figure 4: Number of patients who were off or on minimal corticosteroid

42.0%

achieved CR at 18 months. In patients treated with cyclophosphamide (followed by

relapse. The efficacy and safety of rituximab in maintenance therapy has not been

A total of 23/99 (23%) rituximab-treated patients from the induction of remission trial tested

at screening. There was no apparent negative impact of the presence of ADA on safety or

A total of 117 patients (88 with GPA, 24 with MPA, and 5 with renal-limited ANCA-associated

8 months after randomization. Prednisone dose tapering and the decision to stop prednisone

patients with rituximab starting from month 2 and was maintained up to month 28 (Figure 3).

0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30

Survival Time

(Months)

was required for all patients with CD4+ T-lymphocyte counts less than 250 per cubic (p=0.0005).

treatment after month 18 were left at the investigator's discretion.

Figure 3: Cumulative incidence over time of first major relapse

The primary outcome measure was the rate of major relapse at month 28.

positive for ADA by 18 months. None of the 99 rituximab-treated patients were ADA positive

				•		/ 40 · · · / · · · · · · · · · · · · · · ·			
rituxin (n = 9		= 98)	ntment Difference (rituximab- clophosphamide)		40 -	(≤ 10 mg/day) therapy of Treatment Group: ———————————————————————————————————	over time		
63.69	% 53	3.1%	10.6% 95.1% ^b CI -3.2%, 24.3%) ^a	atients	30 -	Treatment (11 - 50)			
d non-inf	on emonstrated since eriority margin (− 2	20%).	%) was higher than the account for an interim	ber of P	25 - 20 - 15 - 10 -				
nplete re	mission at 6-month	ns by disease status			0-		_++		
osed	rituximab n=99 n=48	Cyclophosphamide n=98 n=48	Difference (CI 95%)		Q	, 8- 8, 8, 6, 6, 6, 6, 6, 6, 6, 6, 6, 6, 6, 6, 6,	visit	Chich the the ten ten te	AN SORY

Post-hoc retrospective laboratory evaluation A total of 19/34 (56%) patients with PV, who were treated with rituximab, tested positive for ADA antibodies by 18 months. The clinical relevance of ADA formation in rituximab-treated PV patients is unclear.

Prednisone

34 (89.5%)

10 (27.8%) < 0.0001 61.7% (38.4, 76.5)

PV Study 2 (Study WA29330) In a randomized, double-blind, double-dummy, active-comparator, multicenter study, the

Rituximab has shown to be highly specific to the CD20 antigen on B cells. Toxicity studies efficacy and safety of rituximab compared with mycophenolate mofetil (MMF) were in cynomolgus monkeys have shown no other effect than the expected pharmacological evaluated in patients with moderate-to-severe PV receiving 60-120 mg/day oral prednisone or equivalent (1.0-1.5 mg/kg/day) at study entry and tapered to reach a dose of 60 or 80 mg/day by Day 1. Patients had a confirmed diagnosis of PV within the previous 24 months and evidence of moderate-to-severe disease (defined as a total Pemphigus Disease Area administered on Day 1, Day 15, Week 24 and Week 26 or oral MMF 2 g/day for 52 weeks in combination with 60 or 80 mg oral prednisone with the aim of tapering to 0 mg/day prednisone

MHS) of the SF-36. Further, a significantly higher proportion of patients achieved MCIDs months after the first course of rituximab. The limited data from the present trial preclude rituximab compared with MMF in achieving sustained complete remission defined as achieving healing of lesions with no new active lesions (i.e., PDAI activity score of 0) while on 0 mg/day prednisone or equivalent, and maintaining this response for at least 16 Continued immunosuppressive therapy may be especially appropriate in patients at risk for consecutive weeks, during the 52-week treatment period. relapses (i.e. with history of earlier relapses and GPA, or patients with reconstitution of PV Study 2 Results

> been achieved, continued immunosuppressive therapy may be considered to prevent course of oral corticosteroids in achieving CRoff corticosteroid ≥ 16 weeks at Week 52 in PV patients (Table 19). The majority of patients in the mITT population were newly diagnosed 6.1 List of excipients (74%) and 26% of patients had established disease (duration of illness ≥ 6 months and received prior treatment for PV). Table 19 Percentage of PV Patients Who Achieved Sustained Complete Remission Off

Corticosteroid Therapy for 16 Weeks or More at Week 52 (Modified Intent-to-Treat Population) Rituximab MMF Difference (N=63) (95% CI) 25 (40.3%) 6 (9.5%) 30.80% vasculitis) in disease remission were randomized to receive azathioprine (59 patients) or Number of responders (14.70%, 45.15%)

> Patients with established 6 (42.9%) 2 (10.5%) MMF = Mycophenolate mofetil, CI = Confidence Interva Newly diagnosed patients = duration of illness < 6 months or no prior treatment for PV Patients with established disease = duration of illness ≥ 6 months and received prior Cochran-Mantel-Haenszel test is used for p-vali

Newly diagnosed patients 19 (39.6%) 4 (9.1%)

Glucocorticoid exposure The cumulative oral corticosteroid dose was significantly lower in patients treated with All patients were followed until month 28 (10 or 6 months, respectively, after the last The median (min, max) cumulative prednisone dose at Week 52 was 2775 mg (450, rituximab infusion or azathioprine dose). Pneumocystis jirovecii pneumonia prophylaxis 22180) in the rituximab group compared to 4005 mg (900, 19920) in the MMF group

Disease flare The total number of disease flares was significantly lower in patients treated with rituximab compared to MMF (6 vs. 44, p < 0.0001) and there were fewer patients who had at least At month 28, major relapse (defined by the reappearance of clinical and/or laboratory signs one disease flare (8.1% vs. 41.3%). of vasculitis activity ([BVAS] > 0) that could lead to organ failure or damage or could be life Laboratory evaluations

threatening) occurred in 3 patients (5%) in the <u>rituximab</u> group and 17 patients (29%) in the azathioprine group (p=0.0007). Minor relapses (not life threatening and not involving major rituximab-treated PV patients tested positive for ADA. There was no apparent negative Store in a refrigerator (2°C – 8°C). damage) occurred in seven patients in the rituximab group (12%) and eight patients impact of the presence of ADA on safety or efficacy in PV Study 2. 5.2 Pharmacokinetic properties The cumulative incidence rate curves showed that time to first major relapse was longer in

> Based on a population pharmacokinetic analysis in 298 NHL patients who received single or multiple infusions of rituximab as a single agent or in combination with CHOP therapy (applied rituximab doses ranged from 100 to 500 mg/m²), the typical population estimates of nonspecific clearance (CL₂) likely contributed by B cells or tumour burden, and central compartment volume of distribution (V1) were 0.14 L/day, 0.59 L/day, and 2.7 L, of rituximab in 50 ml. Packs of 1 vial. respectively. The estimated median terminal elimination half-life of rituximab was 22 days
>
> Each box of Rixathon 100 mg contains 2 vials. (range, 6.1 to 52 days). Baseline CD19-positive cell counts and size of measurable tumour Each box of Rixathon 500 mg contains 1 vial. lesions contributed to some of the variability in CL₂ of rituximab in data from 161 patients given 375 mg/m² as an intravenous infusion for 4 weekly doses. Patients with higher 6.6 Special precautions for disposal and other handling CD19-positive cell counts or tumour lesions had a higher CL₂. However, a large component of inter-individual variability remained for CL₂ after correction or CD19-positive cell counts and tumour lesion size. V₁ varied by body surface area (BSA)
>
> Aseptic preparation BSA (1.53 to 2.32 m²) and concurrent CHOP therapy, respectively, were relatively small. Age, gender and WHO performance status had no effect on the pharmacokinetics of covariates is not expected to result in a meaningful reduction in its pharmacokinetic for the safe handling of intravenous agents.

Adult Non-Hodgkin's lymphoma

Rheumatoid arthritis

Rituximab, administered as an intravenous infusion at a dose of 375 mg/m² at weekly intervals for 4 doses to 203 patients with NHL naive to rituximab, yielded a mean C_{max} successive infusion, spanning from a mean of 243 µg/mL (range, 16 – 582 µg/mL) after the first infusion to 550 μg/mL (range, 171 – 1177 μg/mL) after the eighth infusion. The pharmacokinetic profile of rituximab when administered as 6 infusions of 375 mg/m² in local requirements. combination with 6 cycles of CHOP chemotherapy was similar to that seen with rituximab

7. LICENSE HOLDER AND IMPORTER'S NAME AND ADDRESS Azathioprine | 59 | 56 | 52 | 50 | 47 | 47 | 44 | 44 | 42 | 41 | 40 | 39 | 36 | 34 | 0 58 56 56 56 55 54 54 54 54 54 54 54 52 50 0

Chronic lymphocytic leukaemia Rituximab was administered as an intravenous infusion at a first-cycle dose of 375 mg/m² 8. MARKETING AUTHORISATION NUMBER 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 μ g/mL (range, 97 – 764 A total of 6/34 (18%) of rituximab treated patients from the maintenance therapy clinical trial developed ADA. There was no apparent negative impact of the presence of ADA on μg/mL) after the fifth 500 mg/m² infusion and the mean terminal half-life was 32 days (range,

Following two intravenous infusions of MabThera at a dose of 1000 mg, two weeks apart, the The efficacy and safety of rituximab in combination with short-term, low-dose glucocorticoid mean terminal half-life was 20.8 days (range, 8.58 to 35.9 days), mean systemic clearance was (prednisone) therapy were evaluated in newly diagnosed patients with moderate to severe 2000 (23 L/day), and mean steady-state distribution volume was 4.6 I pemphigus (74 pemphigus vulgaris [PV] and 16 pemphigus foliaceus [PF]) in this randomised, open-label, controlled, multicenter study. Patients were between 19 and 79 values for systemic clearance and half-life, 0.26 L/day and 20.4 days, respectively. Population years of age and had not received prior therapies for pemphigus. In the PV population, 5

pharmacokinetic analysis revealed that BSA and gender were the most significant covariates to (13%) patients in the rituximab group and 3 (8%) patients in the standard prednisone group had moderate disease and 33 (87%) patients in the rituximab group and 33 (92%) patients in the standard-dose prednisone group had severe disease according to disease severity adjustment is not required. No pharmacokinetic data are available in patients with hepatic or Patients were stratified by baseline disease severity (moderate or severe) and randomised

The pharmacokinetics of rituximab were assessed following two intravenous (IV) doses of 500 1:1 to receive either rituximab and low-dose prednisone or standard-dose prednisone.

Patients randomised to the rituximab group received an initial intravenous infusion of 1000 mg and 1000 mg on Days 1 and 15 in four studies. In all these studies, rituximab proportional over the limited dose range studied. Mean Complete the part of the proportional prop pharmacokinetics were dose proportional over the limited dose range studied. Mean C_{max} for mg rituximab on Study Day 1 in combination with 0.5 mg/kg/day oral prednisone tapered off over 3 months if they had moderate disease or 1 mg/kg/day oral prednisone tapered off over 6 months if they had severe disease, and a second intravenous infusion of 1000 mg on Study Day 15. Maintenance infusions of rituximab 500 mg were administered at months

12 and 18. Patients randomised to the standard-dose prednisone group received an initial the 2 × 1000 mg dose. Mean terminal elimination half-life ranged from 15 to 16 days for the 1 mg/kg/day oral prednisone tapered off over 12 months if they had moderate disease or 2 x 500 mg dose group and 17 to 21 days for the 2 × 1000 mg dose group. Mean C_{max} was 16 mg/kg/day oral prednisone tapered off over 18 months if they had severe disease. to 19% higher following second infusion compared to the first infusion for both doses Patients in the rituximab group who relapsed could receive an additional infusion of The pharmacokinetics of rituximab were assessed following two IV doses of 500 mg and the majority of patients. The presence of ADA may be associated with worsening of infusion rituximab 1000 mg in combination with reintroduced or escalated prednisone dose.

1000 mg upon re-treatment in the second course. Mean C_{max} for serum rituximab following Maintenance and relapse infusions were administered no sooner than 16 weeks following the previous infusion.

Maintenance and relapse infusions were administered no sooner than 16 weeks 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 The primary objective for the study was complete remission (complete epithelialisation and from 377 to 386 µg/mL for the 2 x 1000 mg dose. Mean terminal elimination half-life after the absence of new and/or established lesions) at month 24 without the use of prednisone becapt for two months or months of months of the 2 x 1000 mg dose, we all entitled entitled entitled after the second infusion, following the second course, was 19 days for 2 x 500 mg dose and ranged from 24 to 22 days for the 2 x 4000 mg dose.

PK parameters for rituximab were comparable over the two treatment courses. The pharmacokinetic (PK) parameters in the anti-TNF inadequate responder population, The study showed statistically significant results of rituximab and low-dose prednisone following the same dosage regimen (2 x 1000 mg, IV, 2 weeks apart), were similar with a over standard-dose prednisone in achieving CRoff ≥ 2 months at month 24 in PV patients mean maximum serum concentration of 369 µg/mL and a mean terminal half-life of 19.2 days. Granulomatosis with polyangiitis and microscopic polyangiitis Adult population

Based on the population pharmacokinetic analysis of data in 97 patients with granulomatosis with polyangiitis and microscopic polyangiitis who received 375 mg/m² rituximab once weekly for four doses, the estimated median terminal elimination half-life was 23 days (range, 9 to 49 days). Rituximab mean clearance and volume of distribution were 0.313 L/day (range, 0.116 to 0.726 L/day) and 4.50 L (range 2.25 to 7.39 L) respectively. Maximum concentration during the first 180 days (C_{max}) minimum concentration at Day 180 (C180) and Cumulative area under the curve over 180 days (AUC180) were (median [range]) 372.6 (252.3-533.5) µg/mL, 1 (0-29.3) µg/mL and 10302 (3653- 21874) µg/mL*days, respectively. The PK parameters of rituximab in adult GPA and MPA patients appear similar to what has been observed in rheumatoid arthritis patients.

minimal therapy (prednisone dose of 10 mg or less per day) compared to standard-dose Pemphigus vulgaris prednisone patients over the 24-month treatment period shows a steroid-sparing effect of The PK parameters in adult PV patients receiving rixathon 1000 mg at Days 1, 15, 168, and 182 are summarized in Table 20.

Parameter	Infusio	n Cycle
	1st cycle of 1000 mg Day 1 and Day 15 N=67	2nd cycle of 1000 i Day 168 and Day 1 N=67
Terminal Half-life (days)		
Median	21.0	26.5
(Range)	(9.3-36.2)	(16.4-42.8)
Clearance (L/day)		
Mean	391	247
(Range)	(159-1510)	(128-454)
Central Volume of Distribution (L)		
Mean	3.52	3.52
(Range)	(2.48-5.22)	(2.48-5.22)

following the first two rituximab administrations (at day 1 and 15, corresponding to cycle 1), the PK parameters of rituximab in patients with PV were similar to those in patients with GPA/ MPA and natients with RA. Following the last two administrations (at day 168 and 182) corresponding to cycle 2), rituximab clearance decreased while the central volume of 5.3 Preclinical safety data

depletion of B cells in peripheral blood and in lymphoid tissue. Developmental toxicity studies have been performed in cynomolgus monkeys at doses un 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

natally 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 immunisatio 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

B-lymphocytes in addition to PR3-ANCA at monitoring). When remission with rituximab has The study demonstrated the superiority of rituximab over MMF in combination with a tapering 6. PHARMACEUTICAL PARTICULARS

Citric acid monohydrate Polysorbate 80 Water for injections

6.2 Incompatibilities No incompatibilities between Rixathon and polyvinyl chloride or polyethylene bags or infusion sets have been observed.

> Rixathon may be stored at temperatures up to a maximum of 30°C for a single period of up to 7 days, but not exceeding the original expiry date. The new expiry date must be written on the carton. Upon removal from refrigerated storage, Rixathon must not be returned to refrigerated storage. Diluted solution • After aseptic dilution in sodium chloride solution:

The expiry date of the product is indicated on the packging materials.

Chemical and physical stability of Rixathon diluted in 0.9% sodium chloride solution has 30 days at 2°C - 8°C and subsequently 24 hours at room temperature (≤ 25°C). • 7 days at ≤ 30°C, while protected from light.

Chemical and physical stability of Rixathon diluted in 5% glucose solution has been demonstrated for 24 hours at 2°C - 8°C and subsequently 12 hours at room temperature 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 condition

After aseptic dilution in glucose solution

Keep the container in the outer carton in order to protect from light. For storage conditions of the unopened vial outside the refrigerator, see section 6.3. For storage conditions after dilution of the medicinal product, see section 6.3. 6.5 Nature and contents of container

10 mL vial: Colorless tubular glass vial with chlorobutyl rubber stopper containing 100 mg

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

and CHOP therapy. This variability in V. (27.1% and 19.0%) contributed by the range in Aseptic handling must be ensured when preparing the infusion. Preparation should be: - performed under aseptic conditions by trained personnel in accordance with good practice rules especially with respect to the aseptic preparation of parenteral products ituximab. This analysis suggests that dose adjustment of rituximab with any of the tested - prepared in a laminar flow hood or biological safety cabinet using standard precautions

Aseptically withdraw the necessary amount of Rixathon, and dilute to a calculated

following the fourth infusion of 486 µg/mL (range, 77.5 to 996.6 µg/mL). Rituximab was the solution, gently invert the bag in order to avoid foaming. Care must be taken to ensure detectable in the serum of patients 3 – 6 months after completion of last treatment. the sterility of prepared solutions. Since the medicinal product does not contain any anti-Upon administration of rituximab at a dose of 375 mg/m² as an intravenous infusion at microbial preservative or bacteriostatic agents, aseptic technique must be observed. weekly intervals for 8 doses to 37 patients with NHL, the mean C_{max} increased with each

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

Medicine: keep out of reach of childre

Sandoz Pharmaceuticals Israel Ltd., P.O.Box 9015, Tel Aviv, Israel

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