DR. REDDY'S LABORATORIES (PTY) LTD
PROFESSIONAL INFORMATION:
REDDITUX 100 & 500
(concentrate for solution for infusion)

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

REDDITUX 100 concentrate for solution for infusion

REDDITUX 500 concentrate for solution for infusion

WARNINGS

Infusion-related reactions: infusion-related deaths (death within 24 hours of the infusion) have been reported. These events appear as manifestations on an infusion-related complex which include hypoxia, lung infiltration, adult respiratory distress syndrome, myocardial infarction, ventricular fibrillation or cardiogenic shock. Nearly all fatal infusion-related events occurred were associated with the first infusion.

Tumour Lysis Syndrome (TLS): Acute renal failure requiring dialysis with instances of fatal outcome has been reported. Assessment of serum electrolytes and renal function is indicated in patients with rapid decrease in tumour volume.

Severe mucocutaneous reactions: Severe skin reactions such as Toxic Epidermal Necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome, some with fatal outcome, have been reported.

Progressive multifocal leukoencephalopathy (PML): Very rare cases of fatal PML have been reported. Patients must be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML.

Reactivation of hepatitis B: Cases of hepatitis B reactivation and reports of fulminant hepatitis, some of which were fatal have been reported.

Tuberculosis: Serious infections, including fatalities, can occur during therapy with rituximab. A diagnosis of any form of active tuberculosis should be explicitly excluded in patients considered for treatment with REDDITUX.

(See Section 4.4).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of REDDITUX 100 contains 100 mg of rituximab concentrate for solution for infusion.

Each vial of REDDITUX 500 contains 500 mg of rituximab concentrate for solution for infusion.

Excipients with known effects:

REDDITUX 100 and 500 contains 2,27 mmol (or 52,26 mg) and 11,36 mmol (or 261,34 mg) sodium per 10 ml and 50 ml vial respectively.

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear to opalescent; colourless to yellowish solution, essentially free from visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

REDDITUX is indicated for:

Non Hodgkin lymphoma (NHL):

- patients with relapsed or chemo-resistant low grade or follicular, CD20- positive, B-cell non Hodgkin lymphoma;
- previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy;
- patients with follicular lymphoma as maintenance treatment, after response to induction therapy.
- patients with high grade CD20-positive diffuse large B cell non Hodgkin lymphoma in combination with CHOP (cyclophosphamide (C), doxorubicin (H), vincristine (O), prednisolone (P) chemotherapy.

Chronic lymphocytic leukaemia (CLL):

- REDDITUX in combination with fludarabine and cyclophosphamide is indicated for the treatment of patients with previously untreated relapsed/refractory chronic lymphocytic leukaemia (CLL).

Granulomatosis with polyangiitis and microscopic polyangiitis:

- REDDITUX, in combination with glucocorticoids, is indicated for the treatment of patients with severely active Granulomatosis with polyangiitis (GPA, also known as Wegener's granulomatosis) and microscopic polyangiitis (MPA).

Pemphigus vulgaris

- REDDITUX is indicated for the treatment of patients with moderate to severe pemphigus vulgaris (PV).

4.2 Posology and method of administration

REDDITUX should be administered under the close supervision of an experienced healthcare professional, and in an environment where full resuscitation facilities are immediately available (see Section 4.4).

Premedication and prophylactic medications

Premedication consisting of an anti-pyretic and an antihistaminic, e.g., paracetamol and diphenhydramine, should always be administered before each infusion of REDDITUX.

Premedication with glucocorticoids should be considered if REDDITUX is not given in combination with glucocorticoid-containing chemotherapy for treatment of non Hodgkin lymphoma and chronic lymphocytic leukaemia.

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

In patients with granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis in disease remission or pemphigus vulgaris, premedication with 100 mg intravenous methylprednisolone should be completed 30 minutes prior to REDDITUX 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 REDDITUX (the last dose of methylprednisolone may be given on the same day as the first infusion of REDDITUX). This should be followed by oral

prednisone 1 mg/kg/day (not to exceed 80 mg/day, and tapered as rapidly as possible based on clinical need) during and after the 4-week induction course of REDDITUX treatment.

Pneumocystis jirovecii pneumonia (PCP) prophylaxis is recommended for patients with GPA/MPA or PV during and following REDDITUX treatment.

Posology

Low-grade/CD20 positive or follicular B-cell non Hodgkin lymphoma:

Follicular non Hodgkin lymphoma

a) Initial treatment, weekly for 4 doses: The recommended dosage of REDDITUX used as a single agent/mono-therapy for adult patients is 375 mg/m^2 body surface area (BSA), administered as an intravenous infusion once weekly for four doses.

b) Initial treatment, bulky disease, weekly for 4 doses: The recommended dosage of REDDITUX used as a single agent/monotherapy for adult patients is 375 mg/m^2 body surface area (BSA), administered as an intravenous infusion once weekly for four doses.

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

e) Combination therapy: The recommended dosage of REDDITUX in combination with chemotherapy for induction treatment of previously untreated or relapsed/refractory patients with follicular NHL is 375 mg/m^2 body surface area per cycle for 8 cycles (21 days/cycle).

REDDITUX should be administered on day 1 of each chemotherapy cycle, after IV administration of the glucocorticoid component of the chemotherapy, if applicable.

f) Maintenance therapy:

Previously untreated patients after response to induction treatment may receive maintenance

therapy with REDDITUX given at 375 mg/m^2 body surface area once every 2 months until disease progression or for a maximum period of two years (12 infusions).

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

High grade/CD20 positive or diffuse large B-cell non-Hodgkin's lymphoma:

REDDITUX should be used in combination with CHOP chemotherapy (R-CHOP). The recommended dosage is 375 mg/m^2 body surface area, administered on day 1 of each chemotherapy cycle for 8 cycles after IV administration of the glucocorticoid component of CHOP. The other components of CHOP should be given after the administration of REDDITUX.

First infusion: The recommended initial rate for infusion is 50 mg/hr; which can subsequently be escalated in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.

Subsequent infusions: Subsequent doses of REDDITUX can be infused at an initial rate of 100 mg/hr, and increased by 100 mg/hr increments at 30-minute intervals, to a maximum of 400 mg/hr.

Dosage adjustments during treatment

No dose reductions of REDDITUX are recommended. When REDDITUX is given in combination with CHOP or CVP chemotherapy, standard dose reductions for the chemotherapeutic agents should be applied.

Chronic Lymphocytic Leukaemia (CLL)

For CLL patients whose lymphocyte counts are > 25 x $10^9/\ell$ it is recommended to administer prednisone/prednisolone 100 mg IV shortly before infusion with REDDITUX to decrease the rate and severity of acute infusion reactions and/or cytokine release syndrome.

The recommended dosage of REDDITUX in combination with chemotherapy for previously

untreated and relapsed/refractory patients is 375 mg/m^2 body surface area administered on day 0 of the first treatment cycle (the day before chemotherapy) followed by 500 mg/m^2 body surface area administered on day 1 of each subsequent cycle for 6 cycles in total. The chemotherapy should be given after REDDITUX infusion.

Granulomatosis with polyangiitis and microscopic polyangiitis

The recommended dosage of REDDITUX for treatment of GPA and MPA is 375 mg/m^2 body surface area, administered as an IV infusion once weekly for 4 weeks.

Methylprednisolone 1 000 mg IV per day for 1 to 3 days is recommended in combination with REDDITUX to treat severe vasculitis symptoms, followed by oral prednisone 1 mg/kg/day (not to exceed 80 mg/day, and tapered as rapidly as possible per clinical need) during and after REDDITUX treatment.

First infusion: The recommended initial infusion rate for REDDITUX is 50 mg/h; subsequently, the rate can be escalated in 50 mg/h increments every 30 minutes to a maximum of 400 mg/h.

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

Pneumocystis jiroveci pneumonia (PCP) prophylaxis is recommended for patients with GPA and MPA during and following REDDITUX treatment, as appropriate.

Pemphigus vulgaris

The recommended dosage of REDDITUX 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.

Maintenance treatment

A maintenance infusion of 500 mg IV should be administered at months 12 and 18, and then every 6

months thereafter if needed, based on clinical evaluation.

Treatment of relapse

In the event of relapse, patients may receive 1000 mg IV. The healthcare provider should also consider resuming or increasing the patient's glucocorticoid dose based on clinical evaluation. Subsequent infusions may be administered no sooner than 16 weeks following the previous infusion.

Special populations

Children and adolescents: The safety and efficacy of REDDITUX in children below 18 years has not yet been established.

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

Method of Administration

The prepared REDDITUX solution should be administered as an intravenous (IV) infusion through a dedicated line. It should not be administered as an intravenous injection or bolus infusion.

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

REDDITUX is compatible with 0,9 % sodium chloride (normal saline) or 5 % dextrose (D5W) solutions for infusion.

First infusion

The recommended initial rate for infusion is 50 mg/hr; after the first 30 minutes, it can be escalated in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.

Subsequent infusions

Subsequent doses of REDDITUX can be infused at an initial rate of 100 mg/hr, and increased by 100 mg/hr increments at 30 minutes intervals, to a maximum of 400 mg/hr.

4.3 Contraindications

- Hypersensitivity to the active substance (rituximab) or to any of the excipients or to murine proteins.
- Active, severe infections (See Section 4.4).
- Patients in a severely immunocompromised state.
- Severe heart failure (New York Heart Association Class IV) or severe, uncontrolled cardiac disease. (See Section 4.4).

4.4 Special warnings and precautions for use

Progressive Multifocal Leukoencephalopathy (PML)

Very rare cases of fatal PML have been reported following use of rituximab. Patients must be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML. If PML is suspected, further dosing must be suspended until PML has been excluded. The clinician should evaluate the patient to determine if the symptoms are indicative of neurological dysfunction, and if so, whether these symptoms are possibly suggestive of PML. Consultation with a neurologist should be considered as clinically indicated.

If any doubt exists, further evaluation, including MRI scan preferably with contrast, cerebrospinal fluid (CSF) testing for JC Viral DNA and repeat neurological assessments, should be considered.

The physician should be particularly alert to symptoms suggestive of PML that the patient may not notice (e.g., cognitive, neurological or psychiatric symptoms). Patients should also be advised to inform their partner or caregivers about their treatment, since they may notice symptoms that the patient is not aware of.

If a patient develops PML, the dosing of REDDITUX must be permanently discontinued.

Following reconstitution of the immune system in immunocompromised patients with PML, stabilisation or improved outcome has been seen. It remains unknown if early detection of PML and suspension of REDDITUX therapy may lead to similar stabilisation or improved outcome.

Non Hodgkin lymphoma (NHL) and chronic lymphocytic leukaemia (CLL)

Infusion related reactions (IRRs)

Rituximab is associated with infusion-related reactions, which may be related to release of cytokines and/or other chemical mediators. Cytokine release syndrome may be clinically indistinguishable from acute hypersensitivity reactions.

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

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

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

dehydrogenase (LDH) and may be associated with acute respiratory failure and death. The acute respiratory failure may be accompanied by events such as pulmonary 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 and should be treated with increased caution. Patients who develop severe cytokine release syndrome should have their infusion interrupted immediately and should receive aggressive symptomatic treatment. Since initial improvement of clinical symptoms may be followed by deterioration, these patients should be closely monitored until tumour lysis syndrome and pulmonary infiltration have been resolved or ruled out. Further treatment

of patients after complete resolution of signs and symptoms has rarely

resulted in repeated severe cytokine release syndrome.

Patients with a high tumour burden or with a high number (≥ 25 x 10^9/ℓ) of circulating malignant cells such as patients with CLL, who may be at higher risk of especially severe cytokine release syndrome, should be treated with extreme caution. These patients should be very closely monitored throughout the first infusion. Consideration should be given to the use of a reduced infusion rate for the first infusion in these patients or a split dosing over two days during the first cycle and any subsequent cycles if the lymphocyte count is still > 25 x 10^9/ℓ.

Infusion-related adverse reactions of all kinds have been observed in 77 % of patients treated with rituximab (including cytokine

release syndrome accompanied by hypotension and bronchospasm in 10 % of patients) (see Section 4.8). These symptoms are usually reversible with interruption of rituximab infusion and administration of an anti-pyretic, an antihistaminic and occasionally oxygen, intravenous saline or

bronchodilators, and glucocorticoids if required.

Anaphylactic and other hypersensitivity reactions have been reported following the intravenous administration of proteins to patients. In contrast to cytokine release syndrome, true hypersensitivity reactions typically occur within minutes after starting infusion. Medicinal products for the treatment of hypersensitivity reactions, e.g., epinephrine (adrenaline), antihistamines and glucocorticoids, should be available for immediate use in the event of an allergic reaction during administration of REDDITUX. Clinical manifestations of anaphylaxis may appear similar to clinical manifestations of the cytokine release syndrome (described above).

Reactions attributed to hypersensitivity have been reported less frequently than those attributed to cytokine release.

Additional reactions reported in some cases were myocardial infarction, atrial fibrillation, pulmonary oedema and acute reversible thrombocytopenia.

Since hypotension may occur during rituximab

administration, consideration should be given to withholding anti-hypertensive medicines 12 hours prior to the REDDITUX infusion.

Cardiac disorders

Angina pectoris, cardiac arrhythmias such as atrial flutter and fibrillation, heart failure and/or myocardial infarction have occurred in patients treated with rituximab. Therefore, patients with a history of cardiac disease and/or cardiotoxic chemotherapy should be monitored closely.

Haematological toxicities

Although REDDITUX is not myelosuppressive in monotherapy, caution should be exercised when considering treatment of patients with neutrophils < 1,5 x 10^9/ℓ and/or platelet counts < 75 x 10^9/ℓ as

clinical experience in this population is limited. Rituximab has been used in patients who underwent autologous bone marrow transplantation and other risk groups with a presumable reduced bone marrow function without inducing myelotoxicity.

Regular full blood counts, including neutrophil and platelet counts, should be performed during REDDITUX therapy.

Infections

Serious infections, including fatalities, can occur during therapy with rituximab. REDDITUX should not be administered to patients with an active, severe infection (e.g., tuberculosis, sepsis and opportunistic infections, see Section 4.3).

Medical practitioners should exercise caution when considering the use of REDDITUX 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 and reports of fulminant hepatitis, some of which were fatal have been reported in patients receiving rituximab. The majority of these subjects were also exposed to cytotoxic chemotherapy. The reports were confounded by both the underlying disease state and the cytotoxic chemotherapy.

Limited information from one study in relapsed/refractory CLL patients suggests that rituximab treatment may also worsen the outcome of primary hepatitis B infections.

Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with REDDITUX. At minimum this should include HBsAg-status and HBcAb-status. Patients with active hepatitis B disease should not be treated with REDDITUX. 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.

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

Immunisations

The safety of immunisation with live viral vaccines, following rituximab therapy has not been studied for NHL and CLL patients. Vaccination with live virus vaccines is therefore not recommended. Patients treated with REDDITUX may receive non-live vaccinations. However, with non-live vaccines response rates may be reduced. In a non-randomised study, patients with relapsed low-grade NHL who received rituximab monotherapy when compared to healthy untreated controls had a lower rate of response to vaccination with tetanus recall antigen (16 % vs. 81 %) and Keyhole Limpet Haemocyanin (KLH) neoantigen (4 % vs. 76 % when assessed for > 2-fold increase in antibody titre). For CLL patients similar results are assumable considering similarities between both diseases but that has not been investigated in clinical trials.

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

Skin reactions

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

Paediatric population

See section "4.2 Posology and method of administration, Special populations."

Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), and pemphigus vulgaris (PV)

Infusion related reactions

Rituximab is associated with infusion related reactions (IRRs), which may be related to release of cytokines and/or other chemical mediators.

Most infusion events reported were mild to moderate in severity. The most common symptoms were allergic reactions like headache, pruritus, throat irritation, flushing, rash, urticaria, hypertension, and pyrexia. In general, the proportion of patients experiencing any infusion reaction was higher following the first infusion than following the second infusion of any treatment course. The incidence of IRR decreased with subsequent courses (see Section 4.8).

The reactions reported were usually reversible with a reduction in rate, or interruption, of rituximab infusion and administration of an anti-pyretic, an antihistamine, and, occasionally, oxygen, intravenous saline or bronchodilators, and glucocorticoids if required. Closely monitor patients with pre-existing cardiac conditions and those who experienced prior cardiopulmonary adverse reactions. Depending on the severity of the infusion-related reaction and the required interventions, temporarily or permanently discontinue REDDITUX. In most cases, the infusion can be resumed at a 50 % reduction in rate (e.g., from 100 mg/h to 50 mg/h) when symptoms have completely resolved.

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 REDDITUX.

There are no data on the safety of rituximab in patients with moderate heart failure (NYHA class III) or severe, uncontrolled cardiovascular disease. In patients treated with rituximab, the occurrence of pre-existing ischemic cardiac conditions becoming symptomatic, such as angina pectoris, has been observed, as well as atrial fibrillation and flutter. Therefore, in patients with a known cardiac history,

and those who experienced prior cardiopulmonary adverse reactions, the risk of cardiovascular complications resulting from infusion reactions should be considered before treatment with rituximab and patients closely monitored during administration. Since hypotension may occur during REDDITUX infusion, consideration should be given to withholding anti-hypertensive medications 12 hours prior to the REDDITUX infusion.

Cardiac disorders

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

Infections

Based on the mechanism of action of rituximab and the knowledge that B-cells play an important role in maintaining normal immune response, patients may have an increased risk of infection following rituximab therapy. Serious infections, including fatalities, can occur during therapy with rituximab (see Section 4.8). REDDITUX should not be administered to patients with an active, severe infection (e.g., tuberculosis, sepsis and opportunistic infections, see Section 4.3) or severely immunocompromised patients (e.g., where levels of CD4 or CD8 are very low). Medical practitioners should exercise caution when considering the use of REDDITUX in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection, e.g., hypogammaglobulinemia (see Section 4.8). It is recommended that immunoglobulin levels are determined prior to initiating treatment with REDDITUX.

Patients reporting signs and symptoms of infection following REDDITUX therapy should be promptly evaluated and treated appropriately. Before giving a subsequent course of REDDITUX treatment, patients should be re-evaluated for any potential risk for infections.

Very rare cases of fatal progressive multifocal leukoencephalopathy (PML) have been reported following use of rituximab for the treatment of autoimmune diseases including Systemic Lupus Erythematosus (SLE) and vasculitis.

Hepatitis B Infections

Cases of hepatitis B reactivation, including those with a fatal outcome, have been reported in patients with granulomatosis with polyangiitis and microscopic polyangiitis.

Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with REDDITUX. At minimum this should include HBsAg-status and HBcAb-status. Patients with active hepatitis B disease should not be treated with REDDITUX. 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.

Late neutropenia

Measure blood neutrophils prior to each course of REDDITUX, regularly up to 6-months after cessation of treatment and upon signs or symptoms of infection (see Section 4.8).

Skin reactions

Severe skin reactions such as Toxic Epidermal Necrolysis (Lyell's Syndrome) and Stevens-Johnson Syndrome, some with a fatal outcome, have been reported (see Section 4.8). In case of such an event, treatment should be permanently discontinued.

Immunisation

Medical practitioners should review the patient's vaccination status and follow current immunisation guidelines prior to REDDITUX therapy. Vaccination should be completed at least 4 weeks prior to first administration of REDDITUX.

The safety of immunisation with live viral vaccines following rituximab therapy has not been studied.

Therefore, vaccination with live virus vaccines is not recommended whilst on REDDITUX therapy or whilst peripherally B cell depleted.

Patients treated with REDDITUX may receive non-live vaccinations. However, response rates to non-live vaccines may be reduced. Should non-live vaccinations be required whilst receiving rituximab therapy, these should be completed at least 4 weeks prior to commencing the next course of REDDITUX.

Malignancy

Immuno-modulatory medicines may increase the risk of malignancy.

HIV and tuberculosis testing and risks of REDDITUX

A diagnosis of any form of active tuberculosis should be explicitly excluded in patients considered for treatment with REDDITUX. Furthermore, a history of previous tuberculosis, HIV-infection, or a diagnosis of latent TB infection pose a risk for reactivation of tuberculosis disease and appropriate preventive therapy is indicated, regardless of HIV-status. Diagnosis and treatment of latent infection, following national guidelines, should be

initiated prior to use of REDDITUX.

People initiating REDDITUX treatment, who initially tested negative for active or latent tuberculosis, should be systematically tested for latent TB infection during treatment with REDDITUX, and preventive treatment instituted if indicated.

Excipients

REDDITUX 100 and 500 contains 2,27 mmol (or 52,26 mg) and 11,36 mmol (or 261,34 mg) sodium per 10 ml and 50 ml vial respectively. This needs to be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Limited data on possible drug interactions with rituximab is currently available.

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

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

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established.

Pregnancy

IgG immunoglobulins are known to cross the placental barrier.

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

Lactation

It is not known if rituximab is excreted in human milk. However, because maternal IgG is excreted in human milk, and rituximab was detectable in milk from lactating monkeys, women should not breastfeed while being treated with REDDITUX and for 12 months following REDDITUX treatment.

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 treatment with REDDITUX.

Fertility

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

4.7 Effects on ability to drive and use machines

No studies on the effects of rituximab on the ability to drive and use machines have been performed. Pharmacological activity and adverse reactions reported to date suggest that rituximab would have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Experience from non Hodgkin lymphoma (NHL) and chronic lymphocytic leukaemia (CLL) in adults

Summary of the safety profile

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

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

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

The most frequent reported or observed serious adverse drug reactions were:

- Infusion-related reactions (including cytokine-release syndrome, tumour-lysis syndrome),
- Infections
- Cardiovascular events

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

Tabulated list of adverse reactions

The frequencies of ADRs reported with rituximab alone or in combination with chemotherapy are summarised in the tables below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10) uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1000) and very rare (<1/10,000). The ADRs identified only during post-marketing surveillance, and for which a frequency could not be estimated, are listed under "unknown".

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

System Organ Class	*Very Common*	*Common*	*Un-common*	*Rare*	*Very Rare*	*Unknown*[8]
Infections and infestations	bacterial infections, viral infections, +bronchitis	sepsis, +pneumonia, +febrile infection, +herpes zoster, +respiratory tract infection, fungal infections, infections of unknown aetiology, +acute bronchitis, +sinusitis, hepatitis B[1]		serious viral infection[2], *Pneumo-cystis jirovecii*	PML	
Blood and lymphatic system disorders	neutropenia, leukopenia, +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[4], cytokine release syndrome[4], serum sickness,	infusion –related acute reversible thrombocytopenia[4]
Metabolism and nutrition disorders		hyperglycaemia, weight decrease, peripheral oedema, face oedema, increased LDH, hypocalcaemia				
Psychiatric disorders			depression, nervousness			

Nervous system disorders		paraesthesia, hypoesthesia, agitation, insomnia, vasodilatation, dizziness, anxiety	dysgeusia		peripheral neuropathy, facial nerve palsy[5]	Cranial neuropathy, loss of other senses[5]
Eye disorders		lacrimation disorder, conjunctivitis			severe vision loss[5]	
Ear and labyrinth disorders		tinnitus, ear pain				hearing loss[5]
Cardiac disorders		[+]myocardial infarction[4 and 6], arrhythmia, [+]atrial fibrillation, tachycardia, [+]cardiac disorder	[+]left ventricular failure, [+]supraventricular tachycardia, [+]ventricular tachycardia, [+]angina, [+]myocardial ischaemia, bradycardia,	severe cardiac events [4 and 6]	heart failure[4 and 6]	
Vascular disorders		hypertension, orthostatic hypotension, hypotension			vasculitis (predominately cutaneous), leukocytoclastic vasculitis	
Respiratory, thoracic and mediastinal disorders		bronchospasm[4], Respiratory disease, Chest pain, dyspnoea, increased cough, rhinitis	asthma, bronchiolitis obliterans, lung disorder, hypoxia	interstitial lung disease[7]	respiratory failure[4],	lung infiltration
Gastro-intestinal disorders	nausea	vomiting, diarrhoea, abdominal pain, dysphagia, stomatitis, constipation, dyspepsia, anorexia, throat irritation	abdominal enlargement		gastro-intestinal perforation[7]	

Skin and sub-cutaneous 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]	
Musculo-skeletal, connective tissue and bone disorders		hypertonia, myalgia, arthralgia, back pain, neck pain, pain				
Renal and urinary disorders					renal failure[4]	
General disorders and administration site conditions	fever, chills, asthenia, headache	tumour pain, flushing, malaise, cold syndrome, +fatigue, +shivering, +multi-organ failure[4]	Infusion site pain			
Investigations	decreased IgG levels					

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

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

[2] see also section infection below

[3] see also section hematologic adverse reactions below

[4] see also section infusion-related reactions below. Rarely fatal cases reported

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

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

[7] includes fatal cases

The following terms have been reported as adverse events during clinical trials, however, were reported at a similar or lower incidence in the rituximab arms compared to control arms: hematotoxicity, 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 symptoms included flushing, angioedema, bronchospasm, vomiting, nausea, urticaria/rash, fatigue, headache, throat irritation, rhinitis, pruritus, pain, tachycardia, hypertension, hypotension, dyspnoea, dyspepsia, asthenia and features of tumour lysis syndrome. Severe infusion-related reactions (such as bronchospasm, hypotension) occurred in up to 12 % of the cases.

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

Description of selected adverse reactions

Infections

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

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

Haematologic Adverse Reactions

In clinical trials with rituximab monotherapy given for 4 weeks, haematological abnormalities

occurred in a minority of patients and were usually mild and reversible. Severe (grade 3/4) neutropenia was reported in 4,2 %, anaemia in 1,1 % and thrombocytopenia in 1,7 % of the patients. During rituximab maintenance treatment for up to 2 years, leucopenia (5 % vs. 2 %, grade 3/4) and neutropenia (10 % vs. 4 %, grade 3/4) were reported at a higher incidence when compared to observation. The incidence of thrombocytopenia was low (<1, grade 3/4 %) and was not different between treatment arms. In studies with rituximab in combination with chemotherapy, grade 3/4 leucopenia (R-CHOP 88 % vs. CHOP 79 %, R-FC 23 % vs. FC 12 %), neutropenia (R-CVP 24 % vs. CVP 14 %; R-CHOP 97 % vs. CHOP 88 %, R-FC 30 % vs. FC 19 % in previously untreated CLL), pancytopenia (R-FC 3 % vs. FC 1 % in previously untreated CLL) were usually reported with higher frequencies when compared to chemotherapy alone. However, the higher incidence of neutropenia in patients treated with rituximab and chemotherapy was not associated with a higher incidence of infections and infestations compared to patients treated with chemotherapy alone. Studies in previously untreated and relapsed/refractory CLL have established that in up to 25 % of patients treated with R-FC neutropenia was prolonged (defined as neutrophil count remaining below $1x10^9/\ell$ between day 24 and 42 after the last dose) or occurred with a late onset (defined as neutrophil count below $1x10^9/\ell$ later than 42 days after last dose in patients with no previous prolonged neutropenia or who recovered prior to day 42) following treatment with rituximab plus FC. There were no differences reported for the incidence of anaemia. Some cases of late neutropenia occurring more than four weeks after the last infusion of rituximab were reported. In the CLL first-line study, Binet stage C patients experienced more adverse events in the R-FC arm compared to the FC arm (R-FC 83% vs. FC 71 %). In the relapsed/refractory CLL study, grade 3/4 thrombocytopenias was reported in 11 % of patients in the R-FC group compared to 9 % of patients in the FC group.

Cardiovascular adverse reactions

Cardiovascular reactions during clinical trials with rituximab monotherapy were reported in 18,8 % of patients with the most frequently reported events being hypotension and hypertension. Cases of grade 3 or 4 arrhythmia (including ventricular and supraventricular tachycardia) and angina pectoris during infusion were reported. During maintenance treatment, the incidence of grade 3/4 cardiac disorders was comparable between patients treated with rituximab and observation. Cardiac events were reported as serious adverse events (including atrial fibrillation, myocardial infarction, left ventricular failure, myocardial ischemia) in 3 % of patients treated with rituximab compared to <1 % on observation. In studies evaluating rituximab in combination with chemotherapy, the incidence of grade 3 and 4 cardiac arrhythmias, predominantly supraventricular arrhythmias such as tachycardia and atrial flutter/fibrillation, was higher in the R-CHOP group (14 patients, 6,9 %) as compared to the CHOP group (3 patients, 1,5 %). All of these arrhythmias either occurred in the context of a rituximab infusion or were associated with predisposing conditions such as fever, infection, acute myocardial infarction or pre-existing respiratory and cardiovascular disease. No difference between the R-CHOP and CHOP group was observed in the incidence of other grade 3 and 4 cardiac events including heart failure, myocardial disease and manifestations of coronary artery disease. In CLL, the overall incidence of grade 3 or 4 cardiac disorders was low both in the first-line study (4 % R-FC, 3 % FC) and in the relapsed/refractory study (4 % R-FC, 4 % FC).

Respiratory system

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

Neurologic events

During the treatment period, four patients (2 %) treated with R-CHOP, all with cardiovascular risk factors, experienced thromboembolic cerebrovascular accidents during the first treatment cycle. There was no difference between the treatment groups in the incidence of other thromboembolic

events. In contrast, three patients (1,5 %) had cerebrovascular events in the CHOP group, all of which occurred during the follow-up period. In CLL, the overall incidence of grade 3 or 4 nervous system disorders was low both in the first-line study (4 % R-FC, 4 % FC) and in the relapsed/refractory study (3 % RFC, 3 % FC).

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

Gastrointestinal Disorders

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

IgG levels

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

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

patients are unknown.

Skin and subcutaneous tissue disorders:

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

Patient subpopulations -Rituximab monotherapy

Elderly patients (≥ 65 years):

The incidence of ADRs of all grades and grade 3 /4 ADR was similar in elderly patients compared to younger patients (< 65 years).

Bulky disease:

There was a higher incidence of grade 3/4 ADRs in patients with bulky disease than in patients without bulky disease (25,6 % vs. 15,4 %). The incidence of ADRs of any grade was similar in these two groups.

Re-treatment:

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

Patient subpopulations - Rituximab combination therapy

Elderly patients (≥ 65 years)

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

Experience from granulomatosis with polyangiitis and microscopic polyangiitis

Induction of remission

99 patients were treated for induction of remission of GPA and MPA in an innovator's clinical trial with rituximab (375 mg/m^2, once weekly for 4 weeks) and glucocorticoids.

The ADRs listed in Table 2 were all adverse events which occurred at an incidence of ≥ 5 % in the rituximab group and at a higher frequency than the comparator group.

Table 2 Adverse drug reactions occurring at 6-months in ≥ 5 % of patients receiving rituximab for induction of remission of GPA and MPA, and at a higher frequency than the comparator group.

MedDRA System Organ Class ***Adverse Event***	***Rituximab*** ***(n=99)***
Infections and infestations	
Urinary tract infection	7 %
Bronchitis	5 %
Herpes zoster	5 %
Nasopharyngitis	5 %
Blood and lymphatic system disorders	
Thrombocytopenia	7 %
Immune system disorders	
Cytokine release syndrome	5 %
Metabolism and nutrition disorders	
Hyperkalaemia	5 %
Psychiatric disorders	
Insomnia	14 %
Nervous system disorders	

Dizziness	10 %
Tremor	10 %
Vascular disorders	
Hypertension	12 %
Flushing	5 %
Respiratory, thoracic and mediastinal disorders	
Cough	12 %
Dyspnoea	11 %
Epistaxis	11 %
Nasal congestion	6 %
Gastrointestinal disorders	
Diarrhoea	18 %
Dyspepsia	6 %
Constipation	5 %
Skin and subcutaneous tissue disorders	
Acne	7 %
Musculoskeletal and connective tissue disorders	
Muscle spasms	18 %
Arthralgia	15 %
Back pain	10 %
Muscle weakness	5 %
Musculoskeletal pain	5 %
Pain in extremities	5 %
Investigations	
General disorders and administration site conditions	
Peripheral oedema	16 %

Investigations	
Decreased haemoglobin	6 %

Maintenance treatment

In a further clinical study, a total of 57 severe, active GPA and MPA patients in disease remission were treated with rituximab for the maintenance of remission.

Table 3 Adverse drug reactions occurring in ≥ 5 % of patients receiving rituximab for maintenance treatment of GPA and MPA, and at a higher frequency than the comparator group

MedDRA System organ class Adverse reaction	Rituximab (n=57)
Infections and infestations	
Bronchitis	14 %
Rhinitis	5 %
Respiratory, thoracic and mediastinal disorders	
Dyspnoea	9 %
Gastrointestinal disorders	
Diarrhoea	7 %
General disorders and administration site conditions	
Pyrexia	9 %
Influenza-like illness	5 %
Oedema peripheral	5 %
Injury, poisoning and procedural complications	
Infusion-related reactions[1]	12 %
[1] Details on infusion related reactions are provided in the description of selected adverse drug reactions section.	

The overall safety profile was consistent with the well-established safety profile for rituximab in approved autoimmune indications, including GPA/MPA. Overall, 4 % of patients in the rituximab arm experienced adverse events leading to discontinuation. Most adverse events in the rituximab arm were mild or moderate in intensity. No patients in the rituximab arm had fatal adverse events.

The most commonly reported events considered as ADRs were infusion-related reactions and infections.

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

Description of selected adverse drug reactions

Infusion-related reactions

In the clinical trial conducted by innovator studying induction of remission with severe active GPA and MPA, IRRs were defined as any adverse event occurring within 24 hours of an infusion and considered to be infusion-related by investigators in the safety population. Of the 99 patients treated with rituximab, 12 (12 %) experienced at least one IRR. All IRRs were CTC Grade 1 or 2. The most common IRRs included cytokine release syndrome, flushing, throat irritation, and tremor. Rituximab was given in combination with intravenous glucocorticoids which may reduce the incidence and severity of these events.

In the maintenance therapy clinical trial, 7/57 (12 %) patients in the rituximab arm experienced at least one infusion-related reaction. The incidence of IRR symptoms was highest during or after the first infusion (9%) and decreased with subsequent infusions (< 4 %). All IRR symptoms were mild or moderate and most of them were reported from the SOCs Respiratory, Thoracic and Mediastinal Disorders and Skin and Subcutaneous Tissue disorders.

Infections

In the clinical trial on induction of remission, which included 99 rituximab-treated patients, the overall rate of infection was approximately 237 per 100

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

In the maintenance therapy clinical trial, 30/57 (53 %) patients in the

rituximab arm experienced infections. The incidence of all grade infections was similar between the arms. Infections were predominately mild to

moderate. The most common infections in the rituximab arm included upper respiratory tract infections, gastroenteritis, urinary tract infections and herpes zoster. The incidence of serious infections was similar in both arms (approximately 12 %). The most commonly reported serious infection in the rituximab group was mild or moderate bronchitis.

Malignancies

In the clinical trial on induction of remission, the incidence of malignancy in

rituximab treated patients in the granulomatosis with polyangiitis and

microscopic polyangiitis clinical study was 2,00 per 100 patient years at the study common closing date (when the final patient had completed the

follow-up period). On the basis of standardised incidence ratios, the

incidence of malignancies appears to be similar to that previously reported in patients with ANCA-associated vasculitis.

Cardiovascular adverse reactions

In the clinical trial on induction of remission, cardiac events occurred at a rate of approximately 273 per 100 patient years (95 % CI 149 to 470) at the 6-month primary endpoint. The rate of serious cardiac events was 2.1 per 100 patient years (95 % CI 3 to 15). The most frequently reported events were tachycardia (4 %) and atrial fibrillation (3 %).

Neurologic events

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

Hepatitis-B reactivation

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

Hypogammaglobulinaemia

Hypogammaglobulinaemia (IgA, IgG or IgM below the lower limit of normal) has been observed in granulomatosis with polyangiitis and microscopic polyangiitis patients treated with rituximab. The rate of overall infections and serious infections was not increased after the development of low IgA, IgG or IgM.

In the induction of remission clinical trial, 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.

In the maintenance therapy clinical trial, no clinically meaningful differences between the two treatment arms or decreases in total immunoglobulin, IgG, IgM or IgA levels were observed throughout the trial.

Neutropenia

In the induction of remission clinical trial, 24 % of patients in the rituximab group (single course) and 23 % of patients in the cyclophosphamide group developed CTC grade 3 or greater neutropenia. Neutropenia was not associated with an observed increase in serious infection in rituximab-treated patients.

In the maintenance therapy clinical trial, the incidence of all-grade neutropenia was 0 % for Rituximab-treated patients vs. 5 % for azathioprine treated patients.

Skin and subcutaneous tissue disorders

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

Experience from pemphigus vulgaris

Summary of the safety profile

The safety profile of rituximab in combination with short-term, low-dose glucocorticoids in the treatment of patients with pemphigus vulgaris was studied in an innovator's Phase 3, randomised, controlled, multicenter, open-label study in pemphigus patients that included 38 pemphigus vulgaris (PV) patients randomised to the Rituximab group. Patients randomised to the Rituximab group received an initial 1000 mg IV on Study Day 1 and a second 1000 mg IV on Study Day 15. Maintenance doses of 500 mg IV were administered at months 12 and 18. Patients could receive 1000 mg IV at the time of relapse.

The safety profile of Rituximab in patients with PV was consistent with that observed in GPA/MPA

patients.

Tabulated list of adverse reactions

Adverse drug reactions presented in Table 4 were adverse events which occurred at a rate of ≥ 5 % among Rituximab-treated PV patients, with a ≥ 2% absolute difference in incidence between the Rituximab-treated group and the standard-dose prednisone group up to month 24. No patients were withdrawn due to ADRs.

Table 4 Adverse drugs reactions for Rituximab-treated pemphigus vulgaris patients in the clinical study up to month 24

System Organ Class Adverse drug reaction	**Rituximab + low-dose prednisone** **(n = 38)**
Injury, Poisoning and Procedural Complications	
Infusion-related reactions*	58 %
Skin and Subcutaneous Tissue Disorders	
Alopecia	13 %
Pruritus	5 %
Urticaria	5 %
Skin disorder	5 %
Psychiatric Disorders	
Persistent depressive disorder	13 %
Major depression	5 %
Irritability	5 %
Infections and Infestations	
Herpes virus infection	8 %
Herpes zoster	5 %
Oral herpes	5 %

Conjunctivitis	5 %
General Disorders and Administration Site Conditions	
Fatigue	8 %
Pyrexia	5 %
Nervous System Disorders	
Headache	5 %
Dizziness	5 %
Gastrointestinal Disorders	
Abdominal pain upper	5 %
Cardiac Disorders	
Tachycardia	5 %
Musculoskeletal and Connective Tissue Disorders	
Musculoskeletal pain	5 %
Neoplasms Benign, Malignant and Unspecified (incl. cysts and polyps)	
Skin papilloma	5 %
* Infusion-related reactions 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 included headaches, chills, high blood pressure, nausea, asthenia and pain.	

Description of selected adverse reactions

Infusion-related reactions

Infusion-related reactions in the pemphigus vulgaris clinical study were common (58 %). Nearly all infusion-related reactions were mild to moderate. The proportion of patients experiencing an 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 GPA/MPA patients.

Infections

Fourteen patients (37 %) in the Rituximab group experienced treatment-related infections compared to 15 patients (42 %) in the standard-dose prednisone group. The most common infections in the Rituximab group were herpes simplex and zoster infections, bronchitis, urinary tract infection, fungal infection and conjunctivitis. Three patients (8 %) in the Rituximab group experienced a total of 5 serious infections (Pneumocystis jirovecii pneumonia, infective thrombosis, intervertebral discitis, lung infection, Staphylococcal sepsis) and one patient (3 %) in the standard-dose prednisone group experienced a serious infection (Pneumocystis jirovecii pneumonia).

The ADRs listed in Table 5 and SADRs listed in Table 6 are based on clinical trial data obtained from "multi-centre, double-blind, parallel group, randomised comparative clinical trial (RI-01-002) conducted by Dr. Reddy's_between DRL-Rituximab (REDDITUX) and RMP (MabThera) in the treatment of DLBCL in previously untreated patients receiving CHOP".

A total of 151 patients were randomised, of which 76 were assigned to treatment with DRL-Rituximab (REDDITUX) and 75 with RMP, safety data obtained from the reference medicinal product in the same clinical trial is also reported for comparison.

Table 5: Summary of most common related TEAEs (preferred term occurring in ≥ 10 % patients) by MedDRA system organ class and preferred term in patients treated in first line for CD20 positive Diffuse Large B-cell Lymphoma with DRL-Rituximab (REDDITUX) (375 mg/m^2) associated to standard CHOP chemotherapy in every 3 weeks cycles

MedDRA SOC Preferred Term	***DRL-Rituximab Related adverse reactions***	***RMP Related adverse reactions***
Patients with at least 1 treatment-related TEAE	**51 (67,1)**	**39 (52,0)**
Blood and lymphatic system disorders	**38 (50,0)**	27 (36,0)
Neutropenia	29 (38,2)	19 (25,3)
Leukopenia	16 (21,1)	8 (10,7)
Thrombocytopenia	11 (14,5)	11 (14,7)
Anaemia	15 (19,7)	5 (6,7)
Febrile neutropenia	4 (5,3)	10 (13,3)
Metabolism and nutrition disorders	**10 (13,2)**	3 (4,0)
Hyperglycaemia	4 (5,3)	1 (1,3)
Decreased appetite	1 (1,3)	0
Respiratory, thoracic and mediastinal disorders	**2 (2,6)**	4 (5,3)
Cough	1 (1,3)	2 (2,7)
Gastrointestinal disorders	**12 (15,8)**	7 (9,3)
Vomiting	4 (5,3)	3 (4,0)
Nausea	3 (3,9)	1 (1,3)
Abdominal pain	2 (2,6)	1 (1,3)

Skin and subcutaneous tissue disorders	**5 (6,6)**	0
Alopecia	3 (3,9)	0
Musculoskeletal and connective tissue disorders	**2 (2,6)**	1 (1,3)
Back pain	0	0
General disorders and administration site conditions	**10 (13,2)**	12 (16,0)
Pyrexia	5 (6,6)	5 (6,7)
Asthenia	2 (2,6)	4 (5,3)
Pain	0	2 (2,7)
Investigations	**17 (22,4)**	15 (20,0)
White blood cell count decreased	6 (7,9)	14 (18,7)
Neutrophil count decreased	9 (11,8)	9 (12,0)
Weight decreased	2 (2,6)	1 (1,3)

Table 6: Summary of treatment-related serious TEAEs by MedDRA system organ class, preferred term in patients treated in first line for CD20 positive Diffuse Large B-cell Lymphoma with DRL-Rituximab (REDDITUX) (375 mg/m^2) associated to standard CHOP chemotherapy in every 3 weeks cycles

MedDRA SOC Preferred Term	***DRL-Rituximab Related serious adverse reactions***	***RMP Related serious adverse reactions***
Total number of treatment-emergent SAE related to the study drug	38	37
Patients with at least 1 treatment-emergent SAE related to the study drug	16 (21,1)	17 (22,7)
Infections and infestations	**9**	**6 (8,0)**
Sepsis	1 (1,3)	2 (2,7)
Lower respiratory tract infection	2 (2,6)	0
Pulmonary tuberculosis	1 (1,3)	1 (1,3)
Diarrhoea infectious	1 (1,3)	0
Gastroenteritis	1 (1,3)	0
Herpes zoster disseminated	0	1 (1,3)
Septic shock	0	1 (1,3)
Upper respiratory tract infection	0	1 (1,3)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**1 (1,3)**	**0**
Tumour pain	1 (1,3)	0
Blood and lymphatic system disorders	**10 (13,2)**	**12 (16,0)**
Febrile neutropenia	4 (5,3)	10 (13,3)
Neutropenia	4 (5,3)	5 (6,7)
Leukopenia	3 (3,9)	0

Anaemia	1 (1,3)	1 (1,3)
Pancytopenia	0	1 (1,3)
Metabolism and nutrition disorders	**2 (2,6)**	**0**
Hypokalaemia	1 (1,3)	0
Tumour lysis syndrome	1 (1,3)	0
Hepatobiliary disorders	1 (1,3)	0
Jaundice	1 (1,3)	0
Vascular disorders	**1 (1,3)**	**0**
Deep vein thrombosis	1 (1,3)	0
Gastrointestinal disorders	**4 (5,3)**	**2 (2,7)**
Vomiting	1 (1,3)	1 (1,3)
Abdominal distension	1 (1,3)	0
Abdominal pain	1 (1,3)	0
Constipation	1 (1,3)	0
Diarrhoea	0	1 (1,3)
Gastritis	1 (1,3)	0
Intestinal obstruction	1 (1,3)	0
General disorders and administration site conditions	**5 (6,6)**	**1 (1,3)**
Pyrexia	3 (3,9)	0
Death	1 (1,3)	0
Disease progression	1 (1,3)	0
Fatigue	0	1 (1,3)
Investigations	**0**	**1 (1,3)**
White blood cell count decreased	0	1 (1,3)

Post-marketing experience

Non Hodgkin Lymphoma (NHL) and Chronic Lymphocytic Leukaemia (CLL):

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

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

Infusion-related reactions

Additional cases of severe infusion-related reactions have been reported during post-marketing use of rituximab**.**

Cardiovascular system

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

Respiratory system

Respiratory failure/insufficiency, lung infiltration in the context of infusion-related reactions (see Section 4.4). In addition to pulmonary events associated with infusions, interstitial ling disease, some with fatal outcome, has been reported.

Blood and lymphatic system

Cases of infusion-related acute reversible thrombocytopenia have been reported.

Skin and Appendages

Severe bullous skin reactions including fatal cases of toxic epidermal necrolysis have been reported.

Nervous system

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

Cases of cranial neuropathy with or without peripheral neuropathy have been reported rarely. Signs and symptoms of cranial neuropathy, such as severe vision loss, hearing loss, loss of other senses, facial nerve palsy occurred at various times up to several months after completion of rituximab therapy.

Body as a whole

Serum sickness-like *reactions have been reported rarely.*

Infections and infestations:

Cases of hepatitis B reactivation have been reported, the majority of which were in subjects receiving rituximab in combination with cytotoxic chemotherapy (see Section 4.4).

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

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 the

patients were HIV positive.

Gastro-intestinal system

Gastro-intestinal perforation, in some cases leading to death, has been observed in patients receiving rituximab in combination with chemotherapy or non Hodgkin lymphoma.

Laboratory Abnormalities

Non Hodgkin Lymphoma

Blood and lymphatic system:

Neutropenia: The onset of neutropenia has occurred more than four weeks after the last infusion of rituximab.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

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

Patients who experience overdose should have immediate interruption of their infusion and be closely monitored.

In the post-marketing setting five cases of rituximab overdose have been reported. Three cases had no reported adverse event. The two adverse events that were reported were flu-like symptoms, with a dose of 1,8 g of rituximab and fatal respiratory failure, with a dose of 2 g of rituximab.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A26 Cytostatic agents

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

L01X C02

Mechanism of action

Rituximab is a chimeric monoclonal antibody that recognizes the human CD20 antigen. It is not, however, on haemopoietic stem cells, pro-B cells, normal plasma cells or other normal tissue. The antigen is expressed on > 95 % of all B cell non Hodgkin Lymphomas (NHLs). This antigen does not internalise upon antibody binding and is not shed from the cell surface. CD20 does not circulate in the plasma as a free antigen and thus, does not compete for antibody binding.

Rituximab binds to the CD20 antigen on B lymphocytes and the Fc domain can recruit immune effector functions to mediate B cell lysis.

Possible mechanisms of effector-mediated cell lysis include complement-dependent cytotoxicity (CDC) resulting from C1q binding, and antibody-dependent cellular cytotoxicity (ADCC).

Rituximab binding to CD 20 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 within 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).

Peripheral blood B cell counts begin to increase from week 24 and evidence for repopulation is observed in the majority of patients 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 Granulomatosis with polyangiitis (Wegener's) (GPA) and Microscopic polyangiitis (MPA) patients, peripheral blood CD19 B-cells were depleted to less than 10 cells/µℓ, following the first two infusions of rituximab, and remained at that level in most patients through month 6 timepoint. The majority of patients (81 %) showed signs of B cell return, which counts > 10 cells/µℓ by month 12, increasing to 87 % by month 18.

5.2 Pharmacokinetic properties

Elimination and distribution

Non Hodgkin lymphoma (NHL)

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/m^2), the typical population estimates of nonspecific clearance (CL_1), specific clearance (CL_2) likely contributed by B cells or tumour burden, and central compartment volume of distribution (V1) were 0,14 ℓ/day, 0,59 ℓ/day, and 2,7 ℓ/day, respectively. The

estimated median terminal elimination half-life of rituximab was 22 days (range, 6,1 to 52 days). Baseline CD19- positive cell counts and size of measurable tumour lesions contributed to some of the variability in CL_2 of rituximab in data from 161 patients given 375 mg/m^2 as an intravenous infusion for 4 weekly doses.

Patients with higher CD19-positive cell counts or tumour lesions had a higher CL_2. However, a large component of inter-individual variability remained for CL_2 after correction for CD19-positive cell counts and tumour lesion size. V1 varied by body surface area (BSA) and CHOP therapy. This variability in V1 (27,1 % and 19,0 %) contributed by the range in BSA (1,53 to 2,32 m^2) and concurrent CHOP therapy, respectively, were relatively small. Age, gender, race and WHO performance status had no effect on the pharmacokinetics of rituximab. This analysis suggests that dose adjustment of rituximab with any of the tested covariates is not expected to result in a meaningful reduction in its pharmacokinetic variability.

Rituximab, administered as an intravenous infusion at a dose of 375 mg/m^2 at weekly intervals for 4 doses to 203 patients with NHL naive to rituximab, yielded a mean C_{max} following the fourth infusion of 486 µg/mℓ (range, 77,5 to 996,6 µg/mℓ). Rituximab was detectable in the serum of patients 3 to 6 months after completion of last treatment.

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Upon administration of rituximab at a dose of 375 mg/m^2 as an intravenous infusion at weekly intervals for 8 doses to 37 patients with NHL, the mean C_{max} increased with each successive infusion, spanning from a mean of 243 µg/mℓ (range, 16 to 582 µg/mℓ) after the first infusion to 550 µg/mℓ (range, 171 to 1177 µg/mℓ) after the eighth infusion.

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

Chronic lymphocytic leukaemia

Rituximab was administered as an IV infusion at a first-cycle dose of 375 mg/m^2 increased to 500 mg/m^2 each cycle for 5 doses in combination with fludarabine and cyclophosphamide in CLL patients. The mean C_{max} (N=15) was 408 µg/mℓ (range, 97 to 764 µg/mℓ) after the fifth 500 mg/ m^2 infusion and the mean terminal half-life was 32 days (range, 14 to 62 days).

Granulomatosis with polyangiitis and microscopic polyangiitis

Based on the population pharmacokinetic analysis of data in 97 GPA and MPA patients who received 375 mg/m^2 rituximab once a week for 4 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 of 0,116 to 0,726 ℓ/day) and 4,50 ℓ (range of 2,25 to 7,39 ℓ) respectively.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polysorbate 80, sodium chloride, sodium citrate dihydrate and water for injection.

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial:

3 years

Storage of reconstituted vials

The prepared infusion solution is physically and chemically stable for 48 hours at 2 °C to 8 °C and subsequently 48 hours at room temperature (25 °C).

From a microbiological point of view, the prepared infusion solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should normally not be longer than 48 hours at 2 °C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Storage of unopened vials

Store vials in a refrigerator between 2 °C to 8 °C. Protect vials from light. Do not freeze. Store in the outer carton until required for use.

Storage of reconstituted vials

See Section 6.3.

6.5 Nature and contents of container

REDDITUX 100: clear USP Type I 10 ml glass vials. The vials are closed with 20 mm grey butyl rubber stoppers laminated with a fluoro-polymer coating. The stoppers are smooth-finished, with a small cavity at the centre. Stoppered vials are capped with 20 mm, flip-off seals. The aluminium seal completely covers the rubber stopper and is capped with an orange polypropylene disc.

REDDITUX 500: clear USP Type I 50 ml glass vials. The vials are closed with 20 mm grey butyl rubber stoppers laminated with a fluoro-polymer coating. The stoppers are smooth-finished, with a small cavity at the centre. Stoppered vials are capped with 20 mm, flip-off seals. The aluminium seal

completely covers the rubber stopper and is capped with an orange polypropylene disc.

6.6 Special precautions for disposal and other handling

Withdraw the required amount of REDDITUX under aseptic conditions and dilute to a calculated rituximab concentration of 1 to 4 mg/ml in an infusion bag containing sterile, non-pyrogenic 0,9 % normal saline solution or 5 % dextrose solution (D5W) for infusion. To mix the solution, gently invert the bag to avoid foaming. Care must be taken to ensure the sterility of prepared solutions. Since the medicine does not contain any anti-microbial preservative or bacteriostatic agents, aseptic technique must be observed. Parental medications should be inspected visually for particulate matter or discolouration prior to administration.

Any unused medicinal product or waste material should be disposed of.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Dr. Reddy's Laboratories (Pty) Ltd.

Block B, 204 Rivonia Road

Morningside

Sandton

2057

8. REGISTRATION NUMBERS

REDDITUX 100: 56/26/0286

REDDITUX 500: 56/26/0287

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

31 May 2022