PROFESSIONAL INFORMATION FOR RITUXIMAB CIPLA

SCHEDULING STATUS

S4

WARNING

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

Tumour Lysis Syndrome (TLS): Acute renal failure requiring dialysis with instances of fatal outcome has been reported in the setting of TLS. Assessment of serum electrolytes and renal function is indicated in patients with rapid decreases in tumour volume. See **section 4.4.**

Severe mucocutaneous reactions: Severe, including fatal, mucocutaneous reactions can occur in patients receiving RITUXIMAB CIPLA (see section 4.4)

Progressive multifocal leukoencephalopathy (PML): Progressive Multifocal Leukoencephalopathy (PML), including fatal PML, can occur in patients receiving (see section 4.4. and 4.8)

Hepatitis B Virus (HBV) Reactivation: HBV reactivation can occur in patients treated with RITUXAN, in some cases resulting in fulminant hepatitis, hepatic failure, and death. Screen all patients for HBV infection before treatment initiation and monitor patients during and after treatment with RITUXAN. Discontinue RITUXAN and concomitant medications in the event of HBV reactivation (see **section 4.4**).

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 RITUXIMAB CIPLA (See **Section 4.4**).

1. NAME OF THE MEDICINE

RITUXIMAB CIPLA (100 mg/10 mL concentrate for solution for infusion)

RITUXIMAB CIPLA (500 mg/50 mL concentrate for solution for infusion)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each RITUXIMAB CIPLA 100 mg/10mL contains 100 mg (in 10 mL) of rituximab concentrate solution for infusion.

Contains 90 mg of sodium chloride and 73,5 mg of sodium citrate dihydrate

Each RITUXIMAB CIPLA 500 mg/50 mL contains 500 mg (in 50 mL) of rituximab concentrate solution for infusion.

RITUXIMAB CIPLA is expressed from a clonal Chinese Hamster Ovary (CHO) cell line that was developed using the Chinese Hamster Elongation Factor 1 (CHEF1) expression system. The construction of CHEF1 vectors and engineered CHO cell line were designed to express RITUXIMAB CIPLA.

Contains 450,0 mg of sodium chloride and 367,5 mg of sodium citrate dihydrate.

Sugar free.

For the full list of excipients, see **section 6.1.**

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion

RITUXIMAB CIPLA 100 mg/10mL is a clear or slightly opalescent, colourless or slightly yellow liquid, free of visible particles.

RITUXIMAB CIPLA 500 mg/50mL is a clear or slightly opalescent, colourless or slightly yellow liquid, free of visible particles.

RITUXIMAB CIPLA is made up of a protein concentration of 10 mg/mL and filled into two different vial sizes of 10 mL and 50 mL nominal volumes, containing either 100 mg and 500 mg of Rituximab biosimilar respectively.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Non-Hodgkin's Lymphoma

RITUXIMAB CIPLA is indicated for the treatment of:

- Patients with relapsed or chemo-resistant low-grade or follicular, CD20-positive, B-cell non-Hodgkin's 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's lymphoma in combination with CHOP (Cyclophosphamide - C, Doxorubicin - H, Vincristine - O, Prednisone - P) chemotherapy.

Chronic Lymphocytic Leukaemia

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

Rheumatoid Arthritis

RITUXIMAB CIPLA in combination with methotrexate is indicated for the treatment of adult patients with active rheumatoid arthritis who have had an inadequate response or intolerance to other disease-modifying anti-rheumatic drugs (DMARDs) including one or more tumour necrosis factor (TNF) inhibitor therapies.

Granulomatosis with polyangiitis (Wegener's) (GPA) and Microscopic polyangiitis (MPA)

RITUXIMAB CIPLA 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).

4.2 Posology and method of administration

Posology

Dose adjustment during treatment

When rituximab is administered in combination with chemotherapy and the dose of the latter needs to be reduced, standard dose reductions must be applied, but reductions in the dose of rituximab are not recommended.

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

a) Initial treatment, weekly for 4 doses: The recommended dosage of RITUXIMAB CIPLA 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.
b) Initial treatment, bulky disease, weekly for 4 doses: The recommended dosage of RITUXIMAB CIPLA 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 RITUXIMAB CIPLA initially have been treated again with RITUXIMAB CIPLA at a dose of 375 mg/m^2 body surface area, administered as an IV infusion once weekly for 4 weeks.

d) Combination therapy: The recommended dosage of RITUXIMAB CIPLA 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).

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

e) Maintenance therapy:

Previously untreated patients after response to induction treatment may receive maintenance therapy with RITUXIMAB CIPLA 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 RITUXIMAB CIPLA 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:

RITUXIMAB CIPLA 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 RITUXIMAB CIPLA. The safety and efficacy has not been established for the combination of rituximab with other chemotherapies in diffuse large B-cell non-Hodgkin lymphoma.

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 RITUXIMAB CIPLA 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 RITUXIMAB CIPLA are recommended. When RITUXIMAB CIPLA is given in combination with CHOP or CVP chemotherapy, standard dose reductions for the chemotherapeutic medicines should be applied.

Chronic Lymphocytic Leukaemia (CLL):

Pre-medication consisting of an analgesic/anti-pyretic (e.g. paracetamol) and an antihistaminic (e.g. diphenhydramine) should always be administered before each infusion of RITUXIMAB CIPLA.

Pre-medication with glucocorticoids should also be considered, particularly if RITUXIMAB CIPLA is not given in combination with steroid-containing chemotherapy.

Prophylaxis with adequate hydration and administration of urico-statics starting 48 hours prior to start of therapy is recommended for CLL patients to reduce the risk of tumour lysis syndrome. For CLL patients whose lymphocyte counts are > 25 x 10^9/L it is recommended to administer prednisone/prednisolone 100 mg IV shortly before infusion with RITUXIMAB CIPLA

to decrease the rate and severity of acute infusion reactions and/or cytokine release syndrome.

The recommended dosage of RITUXIMAB CIPLA 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 RITUXIMAB CIPLA infusion.

Rheumatoid arthritis (RA):

Pre-medication consisting of an analgesic/anti-pyretic (e.g. paracetamol) and an antihistaminic (e.g. diphenhydramine) should always be administered before each infusion of RITUXIMAB CIPLA.

Pre-medication with glucocorticoids should also be administered in order to reduce the frequency and severity of infusion-related reactions. Patients should receive 100 mg IV methylprednisolone to be completed 30 minutes prior to each RITUXIMAB CIPLA infusion.

See **section 4.4.**

A course of RITUXIMAB CIPLA consists of two 1 000 mg IV infusions. The recommended dosage of RITUXIMAB CIPLA is 1 000 mg by IV infusion followed two weeks later by the second 1 000 mg IV infusion.

The need for further courses should be evaluated 24 weeks following the previous course with retreatment given based on residual or disease activity returning to a level above a DAS28-ESR of 2,6 (treatment to remission). Patients may receive further courses no sooner than 16 weeks following the previous course.

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

Second infusion of each course: Subsequent doses of RITUXIMAB CIPLA 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.

Granulomatosis with polyangiitis (Wegener's) (GPA) and Microscopic polyangiitis (MPA):

Pre-medication consisting of an analgesic/anti-pyretic (e.g. paracetamol) and an antihistaminic (e.g. diphenhydramine) should always be administered before each infusion of RITUXIMAB CIPLA.

The recommended dosage of RITUXIMAB CIPLA 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 RITUXIMAB CIPLA 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 RITUXIMAB CIPLA treatment.

First infusion: The recommended initial infusion rate for RITUXIMAB CIPLA 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 RITUXIMAB CIPLA 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.

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.

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

Special populations

Paediatric population

The safety and efficacy of RITUXIMAB CIPLA in children and adolescents (≤ 18 years) have not been established.

Elderly

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

Handling and disposal

Withdraw the required amount of RITUXIMAB CIPLA under aseptic conditions and dilute to a calculated rituximab concentration of 1 - 4 mg/mL in an infusion bag containing sterile, non-pyrogenic 0,9 % normal saline solution or 5 % dextrose solution (D5W) for infusion. To mix the solution, gently invert the bag to avoid foaming. Parenteral medicines should be inspected visually for particulate matter or discolouration prior to administration.

Incompatibilities

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

Method of administration

The prepared RITUXIMAB CIPLA solution should be administered as an IV infusion through a dedicated line.

The prepared infusion solution must not be administered as an IV injection or bolus infusion.

RITUXIMAB CIPLA infusions should be administered in an environment where full resuscitation facilities are immediately available, and under the close supervision of an experienced healthcare professional.

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

Pre-medication consisting of an anti-pyretic and an antihistaminic, e.g. paracetamol and diphenhydramine, should always be administered 30 to 60 minutes prior to each infusion of RITUXIMAB CIPLA.

Pre-medication with glucocorticoids should also be considered, particularly if RITUXIMAB CIPLA is not given in combination with steroid-containing chemotherapy.

Patients should be closely monitored for the onset of cytokine release syndrome. In patients who develop evidence of severe reactions, especially severe dyspnoea, bronchospasm or hypoxia the infusion should immediately be interrupted. The patient should then be evaluated for evidence of tumour lysis syndrome including appropriate laboratory tests and, for pulmonary infiltration, with a chest X-ray. The infusion should not be restarted until complete resolution of all symptoms, and normalisation of laboratory values and chest X-ray findings. At this time, the infusion can be initially resumed at not more than one-half the previous rate. If the same severe adverse reactions occur for a second time the decision to stop the treatment should be seriously considered on a case-by-case basis. See **section 4.4**. Mild or moderate

infusion-related reactions usually respond to a reduction in the rate of infusion. The infusion may be increased upon improvement of symptoms.

4.3 Contraindications

- Hypersensitivity to rituximab or to any of the excipients of RITUXIMAB CIPLA (see **section 6.1**),
- 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 for use in rheumatoid arthritis, granulomatosis with polyangiitis, microscopic polyangiitis and pemphigus vulgaris only (see **section 4.4** [regarding other cardiovascular diseases] and **section 4.8**).
- Pregnancy and lactation.

4.4 Special warnings and precautions for use

Infusion-related adverse events

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

Pre-medication consisting of an analgesic/anti-pyretic and an anti-histaminic, should always be administered before each infusion of RITUXIMAB CIPLA. For RA patients, pre-medication with glucocorticoids should also be administered before each infusion of RITUXIMAB CIPLA, in order to reduce the frequency and severity of infusion-related reactions (see **section 4.2**).

Patients with a high number (> 25 x 10^9/L) of circulating malignant cells or high tumour burden such as patients with CLL and mantle cell lymphoma may be at higher risk of especially severe infusion-related reactions. These patients should be treated with extreme caution and only when other therapeutic alternatives have been exhausted. These patients should be very

closely monitored throughout the first infusion. Consideration should be given to the use of a reduced infusion rate for the first infusion in these patients or a split dosing over two days during the first cycle and any subsequent cycles if the lymphocyte count is still > 25 x 10^9/L. (See **section 4.8**).

For RA patients, most infusion-related events reported in clinical trials were mild to moderate in severity. Severe infusion-related reactions with fatal outcome have been reported in the post-marketing setting (see **section 4.8, Post-Marketing experience, RA section**). Closely monitor patients with pre-existing cardiac conditions and those who experienced prior cardiopulmonary adverse reactions. The most common symptoms were headache, pruritus, throat irritation, flushing, rash, urticaria, hypertension, and pyrexia. In general, the proportion of patients experiencing any infusion reaction was higher following the first infusion of any treatment course than following the second infusion. Subsequent RITUXIMAB CIPLA infusions were better tolerated by patients than the initial infusion. Fewer patients experienced serious IRRs, with most of these reported during the first infusion of the first course (see **section 4.8**).

RITUXIMAB CIPLA is associated in more than 77 % of patients with infusion-related reactions. These may be related to release of cytokine release syndrome and/or chemical mediators. Severe infusion-related reactions may be clinically indistinguishable from hypersensitivity reactions or cytokine release syndrome. Severe infusion-related reactions usually manifest within 30 minutes to 2 hours after starting the first RITUXIMAB CIPLA infusion, and are characterised by pulmonary events and includes, in some cases, rapid tumour lysis and features of tumour lysis syndrome in addition to fever, chills, rigors. Other symptoms include flushing, angioedema, nausea, urticaria/rash, fatigue, headache, throat

irritation, rhinitis, vomiting, and tumour pain. Hypotension and bronchospasm accompanied these symptoms in about 10 % of the cases.

Severe cytokine release syndrome is characterised by severe dyspnoea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema.
Fatal outcomes have been reported for patients who developed severe cytokine release syndrome, occasionally associated with signs and symptoms of tumour lysis syndrome leading to multi-organ failure, respiratory failure and renal failure.
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 (see **section 4.2**) 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.

Most infusion events reported were mild to moderate in severity. The proportion of affected patients decreases with subsequent infusions. Infusion reaction symptoms are usually reversible with a reduction in rate, or interruption of the infusion. Treatment of infusion-related

symptoms with an antihistaminic, antipyretic and a pain reliever is recommended. Additional treatment with oxygen, bronchodilators, glucocorticoids or IV saline may be indicated. In most cases, the infusion can be resumed at a 50 % reduction in rate (e.g. from 100 mg/h to 50 mg/h) when symptoms have completely resolved. Most patients who have experienced non-life-threatening infusion-related reactions have been able to complete the full course of RITUXIMAB CIPLA therapy. Further treatment of patients after complete resolution of signs and symptoms has rarely resulted in repeated severe infusion-related reactions.

Anaphylactic and other hypersensitivity reactions have been reported following the intravenous administration of RITUXIMAB CIPLA to patients. Epinephrine (adrenaline), antihistamines and glucocorticoids should be available for immediate use in the event of a hypersensitivity reaction to RITUXIMAB CIPLA.

In clinical studies 10/990 (1 %) patients with rheumatoid arthritis who received a first infusion of RITUXIMAB CIPLA at any dose experienced a severe reaction during the infusion. RITUXIMAB CIPLA infusions should be administered in an environment where full resuscitation facilities are immediately available, and under the close supervision of an experienced doctor.

In clinical trials (see **section 4.8** – Granulomatosis with polyangiitis (Wegener's) and Microscopic polyangiitis) for GPA and MPA patients, RITUXIMAB CIPLA was given in combination with high doses of glucocorticoids (see **section 4.2**), which may reduce the incidence and severity of these events.

Regarding the management of infusion-related reactions:

- RITUXIMAB CIPLA infusion should be discontinued in patients who develop clinically significant cardiopulmonary events and they should receive medical treatment.

- Patients with pre-existing cardiac and pulmonary conditions or those with prior clinically significant cardiopulmonary adverse events should be monitored during and after subsequent infusions of RITUXIMAB CIPLA.

  In the reported cases, the following factors were more frequently associated with fatal outcomes: women, patients with pulmonary infiltrates, and patients with Chronic Lymphocytic Leukaemia (CLL) or mantle cell lymphoma (see **section 4.8** and **4.4**).

Pulmonary events

Severe pulmonary infusion-related events that resulted in fatal outcomes have been reported during post-marketing use. Pulmonary events have included hypoxia, lung infiltration, and acute respiratory failure. Some of these events have been preceded by severe bronchospasm and dyspnoea. In some cases, symptoms worsened over time, while in others initial improvement was followed by clinical deterioration. Therefore, patients experiencing pulmonary events or other severe infusion-related symptoms should be closely monitored until complete resolution of their symptoms occur. Patients with a history of pulmonary insufficiency or those with pulmonary tumour infiltration may be at greater risk of poor outcome and should be treated with increased caution.

Acute respiratory failure may be accompanied by events such as pulmonary interstitial infiltration or oedema, visible on a chest x-ray. The syndrome usually manifests itself within one or two hours of initiating the first infusion. Patients who experience severe pulmonary events should have their infusion interrupted immediately and should receive aggressive symptomatic treatment. Since initial improvement of clinical symptoms may be followed by deterioration, these patients should be closely monitored until the pulmonary event has resolved.

Rapid tumour lysis

RITUXIMAB CIPLA mediates the rapid lysis of benign and malignant CD20-positive cells. Signs and symptoms (e.g., hyperuricaemia, hyperkalaemia, hypocalcaemia, hyperphosphataemia, acute renal failure, elevated LDH) consistent with tumour lysis syndrome (TLS) have been reported to occur within 30 minutes to 2 hours after the first RITUXIMAB CIPLA infusion in patients with high numbers of circulating malignant lymphocytes. If these signs and symptoms develop, treatment should be stopped immediately. Prophylaxis for TLS should be considered for patients at risk of developing rapid tumour lysis (e.g. patients with a high tumour burden or with a high number (> 25 x $10^9/\ell$) of circulating malignant cells such as patients with CLL and mantle cell lymphoma). Patients at risk of developing rapid tumour lysis should be followed closely and appropriate laboratory monitoring performed. Appropriate medical therapy should be provided for patients who develop signs and symptoms consistent with rapid tumour lysis. Following treatment for and complete resolution of signs and symptoms, subsequent RITUXIMAB CIPLA therapy has been administered in conjunction with prophylactic therapy for TLS in a limited number of cases.

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

Cardiovascular

Since hypotension may occur during RITUXIMAB CIPLA infusion, consideration should be given to withholding antihypertensive medicines 12 hours prior to and throughout RITUXIMAB CIPLA infusion.

There are no data on the safety of RITUXIMAB CIPLA in patients with moderate heart failure (NYHA class III) or severe, uncontrolled cardiovascular disease.

Angina pectoris or cardiac dysrhythmia, such as atrial flutter and fibrillation, heart failure or myocardial infarction have occurred in patients treated with RITUXIMAB CIPLA. Less frequently, patients experienced an exacerbation of pre-existing cardiac conditions such as angina pectoris or congestive heart failure.

Therefore, in patients with a known cardiac history, the risk of cardiovascular complications resulting from infusion reactions should be considered before treatment with RITUXIMAB CIPLA and patients should be closely monitored.

Hypersensitivity reactions

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. Medicines 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 RITUXIMAB CIPLA. Clinical manifestations of anaphylaxis may appear similar to clinical manifestations of the cytokine release syndrome. Reactions attributed to hypersensitivity have been reported less frequently than those attributed to cytokine release.

Monitoring of blood counts

Although RITUXIMAB CIPLA is not myelosuppressive in monotherapy, caution should be exercised when considering treatment of patients with neutrophil counts of < 1,5 x 10^9/L and/or platelet counts of < 75 x 10^9/L, as clinical experience with such patients is limited. RITUXIMAB CIPLA has been used in patients who underwent autologous bone marrow transplantation and in other risk groups with a presumable reduced bone marrow function without inducing myelotoxicity.

Consideration should be given to the need for regular full blood counts, including platelet counts, during monotherapy with RITUXIMAB CIPLA. When RITUXIMAB CIPLA is given in combination with CHOP or CVP chemotherapy, regular full blood counts should be performed according to usual medical practice.

Infections

Based on the mechanism of action of RITUXIMAB CIPLA 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 CIPLA therapy.

Serious infections, including fatalities, can occur during therapy with RITUXIMAB CIPLA. RITUXIMAB CIPLA treatment should not be administered to patients with 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 RITUXIMAB CIPLA in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection (see **section 4.8**).

Patients treated with RITUXIMAB CIPLA should avoid exposure to patients with tuberculosis and should avoid contact with children and adults recently vaccinated with attenuated live vaccines.

Patients who develop infection following RITUXIMAB CIPLA therapy should be promptly evaluated and treated appropriately. It is recommended that immunoglobulin levels are determined prior to initiating treatment with RITUXIMAB CIPLA.

Hepatitis B Infections

In patients with non-Hodgkin's Lymphoma, CLL, RA, GPA and MPA receiving rituximab in combination with cytotoxic chemotherapy, cases of hepatitis B reactivation have been

reported, including reports of fulminant hepatitis, some of which were fatal. The reports were confounded by both the underlying disease state and the cytotoxic chemotherapy.

Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with RITUXIMAB CIPLA as per local guidelines. Patients with active hepatitis B disease should not be treated with RITUXIMAB CIPLA. Patients with positive hepatitis B serology should be monitored and managed following local medical standards to prevent hepatitis B reactivation.

Progressive Multifocal Leuko-encephalopathy (PML)

Cases of progressive multifocal leuko-encephalopathy (PML) have been reported during use of RITUXIMAB CIPLA in NHL, and CLL (See **section 4.8**). The majority of patients had received RITUXIMAB CIPLA in combination with chemotherapy or as part of a haematopoietic stem cell transplant.

Cases of fatal PML have been reported following use of RITUXIMAB CIPLA for the treatment of rheumatoid arthritis and autoimmune diseases including Systemic Lupus Erythematosus (SLE) and Vasculitis.

Several but not all of the reported cases had potential risk factors for PML, including the underlying disease, long term immunosuppressive therapy or chemotherapy. PML has also been reported in patients with autoimmune disease not treated with RITUXIMAB CIPLA. The efficacy and safety of RITUXIMAB CIPLA for the treatment of autoimmune diseases other than rheumatoid arthritis has not been established.

Doctors treating patients with RITUXIMAB CIPLA should consider PML in the differential diagnosis of patients reporting neurological symptoms and consultation with a neurologist should be considered as clinically indicated.

Skin reactions

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

Immunisation

The safety of immunisation with live viral vaccines, following RITUXIMAB CIPLA therapy has not been studied and vaccination with live virus vaccines is not recommended whilst on RITUXIMAB CIPLA or whilst peripherally B-cell depleted.

Patients treated with RITUXIMAB CIPLA may receive non-live vaccinations. However, with non-live vaccines response rates may be reduced.

Rheumatoid Arthritis (RA) & Granulomatosis with polyangiitis (Wegener's) (GPA) and Microscopic polyangiitis (MPA):

The efficacy and safety of RITUXIMAB CIPLA for the treatment of autoimmune diseases other than rheumatoid arthritis and Granulomatosis with polyangiitis (Wegener's) and Microscopic polyangiitis has not been established.

Late neutropenia

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

Methotrexate (MTX) naïve RA populations

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

Concomitant/sequential use of other DMARDs

The concomitant use of RITUXIMAB CIPLA and anti-rheumatic therapies other than those specified under the rheumatoid arthritis indication and directions for use is not recommended. There are limited data from clinical trials to fully assess the safety of the sequential use of other DMARDs (including TNF inhibitors and other biologics) following RITUXIMAB CIPLA (see **section 4.5**). The available data indicate that the rate of clinically relevant infection is unchanged when such therapies are used in patients previously treated with RITUXIMAB CIPLA, however, patients should be closely observed for signs of infection if biologic medicines and/or DMARDs are used following RITUXIMAB CIPLA therapy.

Malignancy

Immunomodulatory medicines may increase the risk of malignancy. On the basis of limited experience with RITUXIMAB CIPLA in rheumatoid arthritis patients (see **section 4.8**) the present data do not seem to suggest any increased risk of malignancy. However, the possible risk for the development of solid tumours cannot be excluded at this time.

HIV and tuberculosis testing and risks of RITUXIMAB CIPLA

A diagnosis of any form of active tuberculosis should be explicitly excluded in patients considered for treatment with RITUXIMAB CIPLA. 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 RITUXIMAB CIPLA.

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

RITUXIMAB CIPLA contains sodium

RITUXIMAB CIPLA contains 90 mg of sodium chloride and 73,5 mg of sodium citrate dihydrate per 10 mL vial and 450,0 mg of sodium chloride and 367,5 mg of sodium citrate dihydrate per 50 mL vial, equivalent to 8,18 % (for 10 mL vial) and 40,875 % (for 50 mL vial) of the of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicines and other forms of interaction

Currently, there are limited data on possible medicines interactions with RITUXIMAB CIPLA.

In CLL patients, co-administration with RITUXIMAB CIPLA 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 CIPLA.

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

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

Women of childbearing potential /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 RITUXIMAB CIPLA.

Pregnancy

RITUXIMAB CIPLA is contraindicated in pregnancy and lactation. Pregnant women should not be treated with RITUXIMAB CIPLA. IgG immunoglobulins are known to cross the placental barrier.

It is not known whether RITUXIMAB CIPLA can cause foetal harm when administered to a pregnant woman or whether it can affect reproductive capacity. B cell levels in human neonates following maternal exposure to RITUXIMAB CIPLA 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 CIPLA during pregnancy. Similar effects have been observed in animal studies. For these reasons RITUXIMAB CIPLA should not be administered to pregnant women unless the possible benefit outweighs the potential risk.

Breastfeeding

Women who are breastfeeding their babies, should not be treated with RITUXIMAB CIPLA.

Whether rituximab is excreted in human milk is not known. However, because maternal IgG is excreted in human milk, RITUXIMAB CIPLA should not be given to women who are breastfeeding.

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 CIPLA on the ability to drive and use machines have been performed, although the pharmacological activity and adverse reactions reported to date suggest that RITUXIMAB CIPLA would have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

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

Summary of the safety profile

The most frequently observed adverse 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 trials in patients with CLL.

The most frequently reported or observed serious adverse reactions were:

- Infusion-related reactions (including cytokine release syndrome, tumor lysis syndrome).
- Infections.
- Cardiovascular reactions.
- Other serious ADRs (adverse reactions) reported include hepatitis B reactivation and PML (see **sections 4.4**).

System organ class	**Adverse reactions**
Infections and infestations	*Frequent:* 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]. *Less frequent:* Serious viral infection[2], *Pneumocystis jirovecii*, PML.

Blood and lymphatic system disorders	*Frequent:* Neutropenia, leucopenia, [+]febrile neutropenia, [+]thrombocytopenia, anaemia, [+]pancytopenia, [+]granulocytopenia. *Less frequent:* Coagulation disorders, aplastic anaemia, haemolytic anaemia, lymphadenopathy, transient increase in serum IgM levels[3]. *Frequency unknown:* late neutropenia[3]
Immune system disorders	*Frequent:* Infusion related reactions, angioedema, hypersensitivity. *Less frequent:* Anaphylaxis, tumour lysis syndrome[4], cytokine release syndrome[4], serum sickness. *Frequency unknown:* Infusion-related acute reversible thrombo-cytopenia[4].
Metabolism and nutrition disorders	*Frequent:* Hyperglycaemia, weight decrease, peripheral oedema, face oedema, increased LDH, hypocalcaemia.
Psychiatric disorders	*Less frequent:* Depression, nervousness
Nervous system disorders	*Frequent:* Paraesthesia, hypoaesthesia, agitation, insomnia, vasodilatation, dizziness, anxiety. *Less frequent:* Dysgeusia, peripheral neuropathy, facial nerve palsy[5]. *Frequency unknown:* Cranial neuropathy, loss of other senses[5].
Eye disorders	*Frequent:* Lacrimation disorder, conjunctivitis *Less frequent:* Severe vision loss[5].
Ear and labyrinth disorders	*Frequent:* Tinnitus, ear pain. *Frequency unknown:* Hearing loss[5].

Cardiac disorders	*Frequent:* [+]Myocardial infarction[4 and 6], arrhythmia, [+]atrial fibrillation, tachycardia, [+]cardiac disorder. *Less frequent:* [+]Left ventricular failure, [+]supraventricular tachycardia, [+]ventricular tachycardia, [+]angina, [+]myocardial ischaemia, bradycardia, severe cardiac disorders [4 and 6], heart failure[4 and 6].
Vascular disorders	*Frequent:* Hypertension, orthostatic hypotension, hypotension. *Less frequent:* Vasculitis (predominately cutaneous), leukocytoclastic vasculitis.
Respiratory, thoracic and mediastinal disorders	*Frequent:* Bronchospasm[4], respiratory disease, chest pain, dyspnoea, increased cough, rhinitis. *Less frequent:* Asthma, bronchiolitis obliterans, lung disorder, hypoxia, interstitial lung disease[7], respiratory failure[4]. *Frequency unknown:* Lung infiltration.
Gastrointestinal disorders	*Frequent:* Nausea, vomiting, diarrhoea, abdominal pain, dysphagia, stomatitis, constipation, dyspepsia, anorexia, throat irritation. *Less frequent:* Abdominal enlargement, gastro-intestinal perforation[7].
Skin and subcutaneous tissue disorders	*Frequent:* Pruritus, rash, [+]alopecia, urticaria, sweating, night sweats, [+]skin disorder. *Less frequent:* Severe bullous skin reactions, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome) [7].

Musculoskeletal, connective tissue disorders	*Frequent:* Hypertonia, myalgia, arthralgia, back pain, neck pain, pain.
Renal and urinary disorders	*Less frequent:* Renal failure[4].
General disorders and administration site conditions	*Frequent:* Fever, chills, asthenia, headache, tumour pain, flushing, malaise, cold syndrome, [+]fatigue, [+]shivering, [+]multi-organ failure[4]. *Less frequent:* Infusion site pain.
Investigations	*Frequent:* Decreased IgG levels.

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

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

[2] see also section infection below

[3] see also section haematologic adverse reactions below

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

[5] signs and symptoms of cranial neuropathy. Occurred at various times up to several months after completion of RITUXIMAB CIPLA 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: haematotoxicity, neutropenic infection, urinary tract infection, sensory disturbance, pyrexia.

Further information on selected, serious adverse drug reactions

Infusion-related reactions

Monotherapy – 4 weeks treatment

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

Combination Therapy (R-CVP in NHL; R-CHOP in DLBCL, R-FC in CLL)

Severe infusion-related reactions occurred in patients at the time of the first treatment cycle with rituximab in combination with chemotherapy. The incidence of infusion-related symptoms decreased substantially with subsequent infusions. Additional reactions reported were dyspepsia, rash, hypertension, tachycardia, features of tumour lysis syndrome. Isolated cases of myocardial infarction, atrial fibrillation, pulmonary oedema and acute reversible thrombocytopenia were also reported.

Infections

Monotherapy 4 weeks treatment

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

Maintenance Treatment (NHL) up to 2 years

Higher frequencies of infections overall, including grade 3 to 4 infections, were observed during rituximab treatment. There was no cumulative toxicity in terms of infections reported over the 2-year maintenance period.

Data from clinical trials included cases of fatal PML in NHL patients that occurred after disease progression and retreatment (see **section 4.4**).

Combination Therapy (R-CVP in NHL; R-CHOP in DLBCL, R-FC in CLL)

No increase in the frequency of infections or infestations was observed. The most common infections were upper respiratory tract infections which were reported for patients on R-CVP and patients receiving CVP. Serious infections were reported in the patients receiving R-CVP and the patients receiving CVP. No life-threatening infections were reported during this study.

In the R-CHOP study the overall incidence of grade 2 to 4 infections was higher in the R-CHOP group than in the CHOP group. Grade 2 to 4 fungal infections were more frequent in the R-CHOP group vs CHOP group; this difference was due to a higher incidence of localised Candida infections during the treatment period.

The incidence of grade 2 to 4 herpes zoster was higher in the R-CHOP group than in the CHOP group. The proportion of patients with grade 2 to 4 infections and/or febrile neutropenia was higher in the R-CHOP group than in the CHOP group. In patients with CLL, the incidence of grade 3 or 4 hepatitis B infection (reactivation and primary infection) was observed in R-FC and none in FC.

Haematologic adverse reactions

Monotherapy 4 weeks treatment

Haematologic abnormalities occurred in a minority of patients and are usually mild and reversible. Severe (grade 3 and 4) thrombocytopenia and neutropenia were reported, and severe anaemia was also reported.

Maintenance Treatment (NHL) up to 2 years

There was a higher incidence of grade 3 to 4 leucopenia and neutropenia in the rituximab arm compared to the observation arm in clinical trials. The incidence of grade 3 to 4 thrombocytopenia was low. In approximately half of the patients with available data on B-cell recovery after the end of rituximab induction treatment, it took 12 months or more for their B-cell levels to return to normal values.

Combination Therapy (R-CVP in NHL; R-CHOP in DLBCL, R-FC in CLL)

During treatment course in studies with rituximab in combination with chemotherapy, grade 3/4 leukopenia and neutropenia were usually reported with higher frequencies when compared to chemotherapy alone. However, the higher incidence of neutropenia in patients treated with rituximab and chemotherapy was not associated with a higher incidence of infections and infestations compared to patients treated with chemotherapy alone. Studies in previously untreated and relapsed/refractory CLL have established that in some cases neutropenia was not prolonged or with a late onset following treatment in the rituximab plus FC group.

No relevant difference between the treatment arms was observed with respect to grade 3 and 4 anaemia or thrombocytopenia.

Cardiovascular events

Monotherapy 4 weeks treatment[j]

Cardiovascular events were reported in patients during clinical trial. The most frequently reported events were hypotension and hypertension. Cases of grade 3 or 4 dysrhythmia (including ventricular and supraventricular tachycardia) and angina pectoris during a rituximab infusion were reported.

Maintenance Treatment (NHL) up to 2 years

In clinical trials, the most frequently reported events were atrial fibrillation, myocardial infarction, left ventricular failure, and myocardial ischaemia.

Combination Therapy (R-CVP in NHL; R-CHOP in DLBCL, R-FC in CLL)

In the R-CHOP study the incidence of grade 3 and 4 cardiac dysrhythmias, predominantly supraventricular dysrhythmias such as tachycardia and atrial flutter/fibrillation, was higher in the R-CHOP group as compared to the CHOP group. All of these dysrhythmias either occurred in the context of a rituximab infusion or were associated with predisposing conditions such as fever, infection, acute myocardial infarction or pre-existing respiratory and cardiovascular disease (see **section 4.4**). 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 and in the relapsed/refractory study.

Respiratory system

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

IgG levels

Maintenance Treatment (NHL) up to 2 years

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

Neurologic events

Combination Therapy (R-CVP in NHL; R-CHOP in DLBCL, R-FC in CLL)

During the treatment period, some of patients 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 CLL, the overall incidence of grade 3 or 4 nervous system disorders was low both in the first-line study and in the relapsed/refractory study.

Subpopulations

Monotherapy – 4 weeks treatment

Elderly patients (≥ 65 years): The incidence of any adverse event and of grade 3 and 4 adverse events was similar in elderly and younger patients.

Combination Therapy

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

Bulky disease

Patients with bulky disease had a higher incidence of grade 3 and 4 adverse events than patients without bulky disease. The incidence of any adverse event was similar in these two groups.

Re-treatment with Monotherapy

The percentage of patients reporting any adverse event and grade 3 and 4 adverse events upon re-treatment with further courses of rituximab was similar to the percentage of patients reporting any adverse event and grade 3 and 4 adverse events upon initial exposure for any adverse event and for grade 3 and 4 adverse events.

Experience from Rheumatoid Arthritis Clinical Trials

The most frequent adverse reaction considered due to receipt of rituximab were infusion-related reactions (IRRs). In addition to adverse reactions seen in RA clinical trials for rituximab, progressive multifocal leuko-encephalopathy (PML) and serum sickness-like reaction have been reported during post-marketing experience (see **section 4.4**).

Summary of adverse drug reactions reported in clinical trials or during post-marketing surveillance occurring in patients with Rheumatoid Arthritis receiving rituximab.

System organ class	**Adverse reactions**
Infections and infestations	*Frequent:* Upper respiratory tract infection, urinary tract infections, bronchitis, sinusitis, gastroenteritis, tinea pedis *Less frequent:* PML, reactivation of hepatitis B.
Blood and lymphatic system disorders	*Frequent:* Neutropenia[1.] *Less frequent:* Late neutropenia[2], serum sickness-like reaction.
Immune system disorders	*Frequent:* [3]Infusion-related reactions (hypertension, nausea, rash, pyrexia, pruritus, urticaria, throat irritation, hot flush, hypotension, rhinitis, rigors, tachycardia, fatigue, oropharyngeal pain, peripheral oedema, erythema).
General disorders and administration site conditions	

	Less frequent: [3]Infusion related reactions (generalized oedema, bronchospasm, wheezing, laryngeal oedema, angioneurotic oedema, generalized pruritus, anaphylaxis, anaphylactoid reaction).
Metabolism and nutrition disorders	*Frequent:* Hypercholesterolemia.
Psychiatric disorders	*Frequent:* Depression, anxiety.
Nervous system disorders	*Frequent:* Headache, Paraesthesia, migraine, dizziness, sciatica.
Cardiac disorders	*Less frequent:* Angina pectoris, atrial fibrillation, heart failure, myocardial infarction, atrial flutter.
Gastrointestinal disorders	*Frequent:* Dyspepsia, diarrhoea, gastro-oesophageal reflux, mouth ulceration, upper abdominal pain.
Skin and subcutaneous tissue disorders	Frequent: Alopecia. *Less frequent:* Toxic epidermal necrolysis (Lyell's syndrome), Stevens-Johnson syndrome[5].
Musculoskeletal, connective tissue disorders	*Frequent:* Arthralgia / musculoskeletal pain, osteoarthritis, bursitis.
Investigations	*Frequent:* Decreased IgM levels [4], decreased IgG levels[4].

[1] Frequency category derived from laboratory values collected as part of routine laboratory monitoring in clinical trials

[2] Frequency category derived from post-marketing data.

[3] Reactions occurring during or within 24 hours of infusion. See also infusion-related reactions below. IRRs may occur as a result of hypersensitivity and/or to the mechanism of action.

[4] Includes observations collected as part of routine laboratory monitoring.

[5] Includes fatal cases

Multiple courses

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

Further information on selected adverse reactions

Infusion-related reactions

The most frequent ADRs following receipt of rituximab in clinical studies were IRRs. Some patients treated with rituximab experienced at least one IRR following first infusion of the first exposure to rituximab. The incidence of IRRs declined with subsequent infusions. There were no CTC Grade 4 IRRs and no deaths due to IRRs in the clinical trials. The proportion of CTC Grade 3 events and of IRRs leading to withdrawal decreased by course and were rare from course 3 onwards. Premedication with intravenous glucocorticoid significantly reduced the incidence and severity of IRRs (see sections **4.2** and **4.4**). Severe IRRs with fatal outcome have been reported in the post-marketing setting.

Infections

The overall rate of infection was approximately 94 per 100 patient years in rituximab treated patients. The infections were predominately mild to moderate and consisted mostly of upper respiratory tract infections and urinary tract infections. The incidence of infections that were serious or required IV antibiotics was approximately 4 per 100 patient years. The rate of

serious infections did not show any significant increase following multiple courses of rituximab. Lower respiratory tract infections (including pneumonia) have been reported during clinical trials, at a similar incidence in the rituximab arms compared to control arms.

Medically serious events reported also include pneumonia.

Cases of progressive multifocal leukoencephalopathy with fatal outcome have been reported following use of rituximab for the treatment of autoimmune diseases. This includes Rheumatoid Arthritis and off-label autoimmune diseases, including Systemic Lupus Erythematosus (SLE) and Vasculitis. In patients with non-Hodgkin's lymphoma receiving rituximab in combination with cytotoxic chemotherapy, cases of hepatitis B reactivation have been reported (see non-Hodgkin's lymphoma). Reactivation of hepatitis B infection has also been reported in RA patients receiving rituximab (see **section 4.4**).

Malignancies

The incidence of malignancy following exposure to rituximab in clinical studies (0,8 per 100 patient years) lies within the range expected for an age and gender matched population.

Cardiovascular

Serious cardiac reactions were reported at a rate of 1.3 per 100 patient years in the rituximab treated patients compared to 1.3 per 100 patient years in placebo treated patients. The proportions of patients experiencing cardiac reactions (all or serious) did not increase over multiple courses.

Neutropenia

Events of neutropenia were observed with rituximab treatment, the majority of which were transient and mild or moderate in severity. Neutropenia can occur several months after the administration of rituximab (see **section 4.4**).

Neutropenic events, including severe late onset and persistent neutropenia, have been rarely reported in the post-marketing setting, some of which were associated with fatal infections.

Skin and subcutaneous tissue disorders

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

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 infections after the development of low IgG or IgM (see **section 4.4**).

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.

Clinical Trial Experience in Granulomatosis with polyangiitis (Wegener's) (GPA) and Microscopic polyangiitis (MPA)

Incidence of Very Common ADRs for rituximab IV-treated GPA and MPA Patients in Clinical Study up to Month 6*

System organ class	**Adverse reactions**
Infections and infestations	*Frequent:* Infections[a].

Gastrointestinal disorders	*Frequent:* Nausea, diarrhoea.
Nervous system disorders	*Frequent:* Headache.
Musculoskeletal and connective tissue disorders	*Frequent:* Muscle spasm, arthralgia.
Blood and lymphatic system disorders	*Frequent:* Anaemia, leucopenia.
General disorders and administration site conditions	*Frequent:* Peripheral oedema, fatigue.
Psychiatric disorders	*Frequent:* Insomnia.
Investigations	*Frequent:* Increased ALT.
Respiratory, thoracic and mediastinal disorders	*Frequent:* Cough, epistaxis, dyspnoea.
Vascular disorders	*Frequent:* Hypertension.
Immune system disorders	*Frequent:* Infusion-related reactions[b].
Skin and subcutaneous tissue disorders	*Frequent:* Rash.

[*]The study design allowed for crossover or treatment by best medical judgment, and 13 patients in each treatment group received a second therapy during the 6-month study period.

a - Most common infections in the rituximab group included upper respiratory tract infections, urinary tract infections, and herpes zoster.

b - Most common terms reported in the rituximab group included cytokine release syndrome, flushing, throat irritation, and tremor.

Incidence of Cardiac Disorders for rituximab IV-treated GPA and MPA patients in Clinical Study up to Month 6*

System organ class	Adverse reactions
Infections and infestations	*Less frequent:* Tachycardia, atrial fibrillation, palpitations.

Further information on selected adverse drug reactions

Infusion-related reactions

Infusion-related reactions (IRRs) in the GPA and MPA clinical study 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. In clinical trials, patients treated with rituximab 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.

Infections

Infections were predominately mild to moderate and consisted mostly of upper respiratory tract infections, herpes zoster and urinary tract infections. The most frequently reported serious infection in the rituximab group was pneumonia.

Malignancies

The incidence of malignancy in rituximab-treated patients in the clinical study was 2,05 per 100 patient years. On the basis of standardised incidence ratios, this malignancy rate appears to be similar to rates previously reported in GPA and MPA populations.

Hepatitis-B reactivation

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.

Laboratory Abnormalities

RA patients

Hypogammaglobulinaemia (IgG or IgM below the lower limit of normal) has been observed in RA patients treated with rituximab. There was no apparent increased rate in overall infections or serious infections after the development of low IgG or IgM.

Events of neutropenia associated with rituximab treatment, the majority of which were transient and mild or moderate in severity, were observed in clinical trials in RA patients after the first course of treatment. Neutropenia can occur several months after the administration of rituximab.

GPA and MPA patients

Hypogammaglobulinaemia (IgA, IgG or IgM below the lower limit of normal) has been observed in GPA and MPA patients treated with rituximab. At 6 months, in a controlled study, some patients in the rituximab group, with normal immunoglobulin levels at baseline, had low IgA, IgG and IgM levels.

Neutropenia: In a study of rituximab in GPA and MPA, some patients in the rituximab group (single course) developed CTC grade 3 or greater neutropenia. The effect of multiple rituximab courses on the development of neutropenia in GPA and MPA patients has not been studied in clinical trials.

Skin and subcutaneous tissue disorders: Toxic Epidermal Necrolysis (Lyell's Syndrome) and Stevens-Johnson Syndrome, some with fatal outcome, have been reported.

Post-marketing experience

Non-Hodgkin's Lymphoma (NHL) and Chronic Lymphocytic Leukaemia (CLL) Patients

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

Infusion-related reactions

Additional cases of severe infusion-related reactions have been reported during post-marketing use of rituximab. Fatal outcomes have been reported for patients who developed severe infusion-related reactions, including cytokine release syndrome, and/or signs and symptoms of tumour lysis syndrome leading to multi-organ failure, respiratory failure, and renal failure. Pulmonary adverse reactions including severe bronchoconstriction and rarely fatalities from respiratory failure have also been reported.

Cardiovascular system

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

Respiratory system

Respiratory failure/insufficiency and lung infiltration in the context of infusion-related reactions (see **section 4.4**). In addition to pulmonary events associated with infusions, interstitial lung 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 reaction including some fatal cases of Toxic Epidermal Necrolysis and Stevens-Johnson Syndrome, have been reported rarely.

Nervous system

Cases of posterior reversible encephalopathy syndrome (PRES) / reversible posterior leukoencephalopathy syndrome (RPLS) have been reported. Signs and symptoms 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, including the patient's underlying disease, hypertension, immunosuppressive therapy and/or chemotherapy.

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

General disorders and administrative site conditions

Serum sickness-like reactions have been reported.

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, either new, reactivation or exacerbation, some of which were fatal, have been reported with rituximab treatment. The majority of patients had received rituximab in combination with chemotherapy or as part of a haematopoietic stem cell transplant. Examples of these serious viral infections are infections caused by the herpes viruses

(cytomegalovirus (CMV), Varicella zoster virus and Herpes simplex virus), JC virus (progressive multifocal leuko-encephalopathy (PML) and Hepatitis C virus.

Progression of Kaposi's sarcoma has been observed in rituximab-exposed patients with pre-existing Kaposi's sarcoma. These cases occurred in non-approved indications and the majority of patients were HIV positive.

Gastro-intestinal system

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

Rheumatoid Arthritis (RA), Granulomatosis with polyangiitis (Wegener's) (GPA) and Microscopic polyangiitis (MPA) patients

Post-marketing

Infections and Infestations: Progressive multifocal leuko-encephalopathy (PML), and reactivation of hepatitis B infection have been reported.

General disorders and administrative site conditions: Serum sickness-like reaction has been reported. Severe infusion-related reactions some with fatal outcome have been reported.

Skin and subcutaneous tissue disorders: Toxic Epidermal Necrolysis and Stevens- Johnson Syndrome some with fatal outcome have been reported and reactivation of hepatitis B infection have been reported.

Blood and lymphatic system disorders: Neutropenic events, including severe late onset and persistent neutropenia, have been reported, some of which were associated with fatal infections.

Laboratory Abnormalities

Non-Hodgkin's Lymphoma

Blood and lymphatic system: Cases of pancytopenia have been reported.

Neutropenia: The onset of neutropenia occurred usually within four weeks after the last infusion of rituximab. In post-marketing studies of rituximab in patients with Waldenstrom's macroglobulinemia, transient increases in serum IgM levels have been observed following treatment initiation, which may be associated with hyper-viscosity and related symptoms. The transient IgM increase usually returned to at least baseline level within 4 months.

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 "Med Safety APP" (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website and to Cipla Medpro (Pty) Ltd. at drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free).

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, monoclonal antibodies, ATC code: L01X C02.

Pharmacological classification: A.26 Cytostatic Agents.

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

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

Peripheral B-cell counts declined to levels below normal following the first dose of rituximab. In patients treated for haematological malignancies B-cell recovery began within 6 months of treatment and generally returning to normal levels within 12 months after completion of therapy, although in some patients this may take longer. In patients with rheumatoid arthritis, the duration of peripheral B-cell depletion was variable. The majority of patients received further treatment prior to B cell repletion. Some patients experienced prolonged B cell depletion.

In Granulomatosis with polyangiitis (Wegener's) (GPA) and Microscopic polyangiitis (MPA) patients, peripheral blood CD19 B-cells 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.

5.2 Pharmacokinetic properties

Pharmacokinetic properties:

Elimination and distribution

Non-Hodgkin's Lymphoma:

Based on a population pharmacokinetic analysis in NHL patients who received single or multiple infusions of rituximab as a single agent or in combination with CHOP therapy, the typical population estimates of non-specific clearance (CL1), specific clearance (CL2) likely contributed by B cells or tumor burden, and central compartment volume of distribution (V1) were 0,14 L /day, 0,59 L/day, and 2,7 L, respectively. The estimated median terminal elimination half-life of rituximab was 22 days (range, 6,1 to 52 days). Baseline CD19-positive cell counts and size of measurable tumour lesions contributed to some of the variability in CL2 of rituximab in data from patients given 375 mg/m^2 as an IV infusion for 4 weekly doses. Patients with higher CD19-positive cell counts or tumour lesions had a higher CL2. However, a large component of inter-individual variability remained for CL2 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 contributed by the range in BSA (1,53 to 2,32 m^2) and concurrent CHOP therapy, respectively, were relatively small. Age, gender, race, and WHO performance status had no effect on the pharmacokinetics of rituximab. This analysis suggests that dose adjustment of rituximab with any of the tested covariates is not expected to result in a meaningful reduction in its pharmacokinetic variability.

Rituximab at a dose of 375 mg/m^2 was administered as an IV infusion at weekly intervals for 4 doses to patients with NHL naive to rituximab. The mean C_{max} following the fourth infusion was 486 µg/mL (range, 77,5 to 996,6 µg/mL). The peak and trough serum levels of rituximab were inversely correlated with baseline values for the number of circulating CD19-positive B-cells and measures of disease burden. Median steady-state serum levels were higher for responders compared with non-responders. Serum levels were higher in patients with International Working Formulation (IWF) subtypes B, C, and D as compared with those with subtype A.

Rituximab was detectable in the serum of patients 3 to 6 months after completion of last treatment.

Rituximab at a dose of 375 mg/m^2 was administered as an IV infusion at weekly intervals for 8 doses to 37 patients with NHL. The mean C_{max} increased with each successive infusion, spanning from a mean of 243 µg/mL (range, 16 – 582 µg/mL) after the first infusion to 550 µg/mL (range, 171 – 1 177 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 (CLL):

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

Rheumatoid Arthritis:

Following two intravenous infusions of rituximab at a dose of 1 000 mg, two weeks apart, the mean terminal half-life was 20,8 days (range, 8,58 to 35,9 days), mean systemic clearance was 0,23 L/day (range, 0,091 to 0,67 L/day), and mean steady-state distribution volume was 4,6 L (range, 1,7 to 7,51 L). Population pharmacokinetic analysis of the same data gave similar mean values for systemic clearance and half-life, 0,26 L/day and 20,4 days, respectively. Population pharmacokinetic analysis revealed that BSA and gender were the most significant covariates to explain inter-individual variability in pharmacokinetic parameters. After adjusting for BSA, male subjects had a larger volume of distribution and a faster clearance than female subjects. The gender-related pharmacokinetic differences are not

considered to be clinically relevant and dose adjustment is not required.

The pharmacokinetics of rituximab were assessed following two IV doses of 500 mg and 1 000 mg on Days 1 and 15 in four studies. In all these studies, rituximab pharmacokinetics were dose proportional over the limited dose range studied. Mean C_{max} for serum rituximab following first infusion ranged from 157 to 171 µg/mL for 2 x 500 mg dose and ranged from 298 to 341 µg/mL for 2 x 1 000 mg dose. Following second infusion, mean C_{max} ranged from 183 to 198 µg/mL for the 2 × 500 mg dose and ranged from 355 to 404 µg/mL for the 2 × 1 000 mg dose. Mean terminal elimination half-life ranged from 15 to 16,5 days for the 2 x 500 mg dose group and 17 to 21 days for the 2 × 1 000 mg dose group. Mean C_{max} was 16 to 19 % higher following second infusion compared to the first infusion for both doses.

The pharmacokinetics of rituximab were assessed following two IV doses of 500 mg and 1000 mg upon re-treatment in the second course. Mean C_{max} for serum rituximab following first infusion was 170 to 175 µg/mL for 2 x 500 mg dose and 317 to 370 µg/mL for 2 x 1 000 mg dose. C_{max} following second infusion, was 207 µg/mL for the 2 x 500 mg dose and ranged from 377 to 386 µg/mL for the 2 x 1 000 mg dose. Mean terminal elimination half-life after the second infusion, following the second course, was 19 days for 2 x 500 mg dose and ranged from 21 to 22 days for the 2 x 1 000 mg dose. PK parameters for rituximab were comparable over the two treatment courses.

The pharmacokinetic parameters in the anti-TNF inadequate responder population, following the same dosage regimen (2 x 1 000 mg, IV, 2 weeks apart), were similar with a mean maximum serum concentration of 369 µg/mL and a mean terminal half-life of 19,2 days.

Rituximab has been shown to reduce the rate of progression of joint damage as measured by x-ray, to improve physical function and to induce major clinical response, when given in combination with methotrexate. The best responses to rituximab are seen in those who have a positive blood test to rheumatoid factor (RF) and/or anti-Cyclic Citrullinated Peptide (anti-CCP). Both tests are commonly positive in rheumatoid arthritis and aid in confirming the

diagnosis.

Granulomatosis with polyangiitis (Wegener's) (GPA) and Microscopic polyangiitis (MPA):

Based on the population pharmacokinetic analysis of data in GPA and MPA patients who received 375 mg/m^2 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. The PK parameters of rituximab in GPA and MPA patients appear similar to what has been observed in RA patients (see section above).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Polysorbate 80 (Tween 80)
- Sodium Chloride
- Sodium Citrate Dihydrate
- Water for injection.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

Diluted medicine

The prepared infusion solution of RITUXIMAB CIPLA in either 0,9 % saline infusion solution or 5 % dextrose infusion solution, the two recommended infusion solution for RITUXIMAB CIPLA is physically and chemically stable for 24 hours at room temperature.

6.4 Special precautions for storage

Store between 2 °C to 8 °C.

Protect vials from sunlight.

Store in outer carton until required for use.

Do not freeze or agitate.

For storage conditions after dilution of the medicinal product, see **section 6.3.**

6.5 Nature and contents of container

RITUXIMAB CIPLA 100 is supplied in a single-use vials containing a sterile, non-pyrogenic concentrate for solution for infusion. The vial consists of a type I borosilicate glass vial sealed with a chlorobutyl stopper with FluroTec® and a blue plastic/aluminium flip-off cap.

RITUXIMAB CIPLA 500 is supplied in a single-use vials containing a sterile, non-pyrogenic concentrate for solution for infusion. The vial consists of a type I borosilicate glass vial sealed with a chlorobutyl stopper with FluroTec® and a dark blue plastic/aluminium flip-off cap.

RITUXIMAB CIPLA 100 mg/10 mL presentation contains two labelled vials of 10 mL each, properly conditioned in a suitable plastic tray placed in a carton box.

RITUXIMAB CIPLA 500 mg/50 mL presentation contains one labelled vial of 50 mL, properly conditioned in a suitable plastic tray placed in a carton box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Make sure that any prepared solutions are sterile. RITUXIMAB CIPLA does not contain antimicrobial preservatives or bacteriostatic medicines. Thus, appropriate aseptic techniques must be used.

Parenteral medicines should be inspected visually for particulate matter and discoloration prior to administration. From a microbiological point of view, the diluted solution prepared for intravenous infusion must be used immediately. If the solution is not used immediately, it can be stored for a maximum of 24 hours inside a 2 to 8 °C fridge. Do not use the solution if it was not prepared in controlled and validated aseptic conditions. Discard any unused portion of RITUXIMAB CIPLA concentrated solution in accordance with local regulations. The same applies to any materials that were in contact with the solution.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Building 9

Parc du Cap

Mispel Street

Bellville

7530

Customer Care: 080 222 6662.

8. REGISTRATION NUMBER(S)

RITUXIMAB 100 CIPLA: 57/26/0217

RITUXIMAB 500 CIPLA: 57/26/0218

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01 April 2025

10. DATE OF REVISION OF THE TEXT

Not applicable.