SUMMARY OF PRODUCTS CHARACTERISTICS

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1.0 Name of the Medicinal Product

Rituximab

2.0 Qualitative and Quantitative Composition

Rituximab in vials is a sterile, clear, colorless and preservative-free solution, available in following dose strengths and its compositions are as follows:

3.0 Pharmaceutical Form

Concentrate for solution for injection in 10 ml and 50 ml single use vials for intravenous (IV) infusion.

4.0 Clinical Particulars

4.1 Therapeutic indications

Rituximab is indicated for the treatment of:

Non-Hodgkin's lymphoma (NHL):

- Male and female adult patients, 18 years or older.
- Patients need to be prescribed and administered Rituximab in order to be evaluable.
- Patients with diagnosed Non-Hodgkin's lymphoma including the following subtypes:
  a) Previously untreated diffuse large B-cell, CD20-positive NHL in combination with CHOP or other anthracycline-based chemotherapy regimens
  b) Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line CVP chemotherapy
  c) Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL as a single agent
  d) Previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to

Rituximab in combination with chemotherapy, as single-agent maintenance therapy.

Patients with diagnosed Chronic Lymphocytic Leukemia (CLL):

- Rituximab in combination with fludarabine and cyclophosphamide (FC) indicated for the treatment of patients with previously untreated and previously treated CD20-positive CLL.

Rheumatoid Arthritis (RA):

- Rituximab in combination with methotrexate is indicated for the treatment of adult patients with moderately- to severely- active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies.

Granulomatosis with polyangiitis and microscopic polyangiitis (GPA & MPA):

- Rituximab in combination with glucocorticoids, is indicated for the induction of remission in adult patients with severe, active granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA).

4.2 Posology and method of administration

Recommended Dose for Non-Hodgkin's Lymphoma (NHL):

The recommended dose is 375 mg/m^2 as an intravenous infusion according to the following schedules:

Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL

Administer once weekly for 4 or 8 doses.

Retreatment for Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL

Administer once weekly for 4 doses.

Previously Untreated, Follicular, CD20-Positive, B-Cell NHL

Administer on Day 1 of each cycle of chemotherapy, for up to 8 doses. In patients with complete or partial response, initiate rituximab maintenance eight weeks following completion of rituximab in combination with chemotherapy. Administer rituximab as a single-agent every 8 weeks for 12 doses.

Non-progressing, Low-Grade, CD20-Positive, B-cell NHL, after first-line CVP chemotherapy

Following completion of 6–8 cycles of CVP chemotherapy, administer once weekly for 4 doses at 6-month intervals to a maximum of 16 doses.

Diffuse Large B-Cell NHL

Administer on Day 1 of each cycle of chemotherapy for up to 8 infusions.

Recommended Dose for Chronic Lymphocytic Leukemia (CLL)

- The recommended dose is 375 mg/m2 the day prior to the initiation of FC chemotherapy, then 500 mg/m2 on Day 1 of cycles 2-6 (every 28 days).
- 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 109/L 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.

Recommended Dose for Rheumatoid Arthritis (RA):

- Administer Rituximab as two-1000 mg intravenous infusions separated by 2 weeks
- Glucocorticoids administered as methylprednisolone 100 mg intravenous or its equivalent 30 minutes prior to each infusion are recommended to reduce the incidence and severity of infusion reactions
- Subsequent courses should be administered every 24 weeks or based on clinical evaluation, but not sooner than every 16 weeks
- Rituximab is given in combination with methotrexate

Recommended Dose for Granulomatosis with polyangiitis and microscopic polyangiitis (GPA & MPA):

- The recommended dose is 375 mg/m2 body surface area, administered as an intravenous infusion once weekly for 4 weeks (four infusions in total).
- Pneumocystis jiroveci pneumonia (PCP) prophylaxis is recommended for patients during and following the treatment, as appropriate.

Administration:

- Administer only as an Intravenous Infusion.
- Do not administer as an intravenous push or bolus.
- Premedicate before each infusion with acetaminophen and an antihistamine. For patients administered Rituximab according to the 90-minute infusion rate, the glucocorticoid component of their chemotherapy regimen should be administered prior to infusion. For RA patients, methylprednisolone 100 mg intravenously or its equivalent is recommended 30 minutes prior to each infusion.

- Rituximab should only be administered by a healthcare professional with appropriate medical support to manage severe infusion reactions that can be fatal if they occur.

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 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.

For previously untreated follicular NHL and DLBCL patients:

If patients did not experience a Grade 3 or 4 infusion related adverse event during Cycle 1, a 90-minute infusion can be administered in Cycle 2 with a glucocorticoid-containing chemotherapy regimen.

Initiate at a rate of 20% of the total dose given in the first 30 minutes and the remaining 80% of the total dose given over the next 60 minutes. If the 90-minute infusion is tolerated in Cycle 2, the same rate can be used when administering the remainder of the treatment regimen (through Cycle 6 or 8).

Patients who have clinically significant cardiovascular disease or who have a circulating lymphocyte count ≥5000/mm^3 before Cycle 2 should not be administered the 90-minute infusion.

Interrupt the infusion or slow the infusion rate for infusion reactions. Continue the infusion at one-half the previous rate upon improvement of symptoms.

Dosage Adjustment

Dosage adjustments during treatment

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

Use in Elderly

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

4.3 Contraindications

Rituximab is contraindicated in patients with:

- Hypersensitivity to the active substance or to murine proteins, or to any of the excipients
- Active, severe infections

- Patients in a severely immunocompromised state.
- Patients who have or have had progressive multifocal leukoencephalopathy (PML)
- Severe heart failure (New York Heart Association Class IV) or severe, uncontrolled cardiac disease

4.4 Special warnings and precautions for use

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

Infusion related reactions

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 associated with set of reactions which includes syndrome of cytokine release, tumour lysis syndrome and anaphylactic and hypersensitivity reactions. They are not specifically related to the route of administration of Rituximab and can be observed with both formulations.

Severe infusion related reactions with fatal outcome have been reported during post-marketing use of the Rituximab intravenous formulation, with an onset ranging within 30 minutes to 2 hours after starting the first Rituximab IV infusion. They were characterized by pulmonary events and in some cases included rapid tumor lysis and features of tumor lysis syndrome in addition to fever, chills, rigors, hypotension, urticaria, angioedema and other.

Severe cytokine release 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 tumor 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 tumor 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.

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). These symptoms are usually reversible with interruption of Rituximab infusion and administration of an anti-pyretic, an

antihistaminic, and, occasionally, oxygen, intravenous saline or bronchodilators, and glucocorticoids if required. Please see cytokine release syndrome above for severe reactions.

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 Rituximab. 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.

Additional reactions reported in some cases were myocardial infarction, atrial fibrillation, pulmonary edema 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 Rituximab infusion.

In rheumatoid arthritis premedication with glucocorticoids should also be administered before each infusion of Rituximab in order to reduce the frequency and severity of IRRs.

Severe IRRs with fatal outcome have been reported in rheumatoid arthritis patients in the post-marketing setting. In rheumatoid arthritis most infusion-related events reported in clinical trials 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. 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 IRR and the required interventions, temporarily or permanently discontinue Rituximab. 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.

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 Rituximab is not myelosuppressive in monotherapy, caution should be exercised when considering treatment of patients with neutrophils < 1.5 x 109/l and/or platelet counts < 75 x 109/l as clinical experience in this population is limited. Regular full blood counts, including neutrophil and platelet counts, should be performed during Rituximab therapy.

Infections

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

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

Cases of hepatitis B reactivation have been reported in subjects receiving Rituximab including fulminant hepatitis with fatal outcome. The majority of these subjects were also exposed to cytotoxic chemotherapy. Hepatitis B virus (HBV) screening should always be performed in patients at risk of infection with HBV before initiation of treatment with Rituximab. At minimum this should include HBsAg-status and HBcAb-status. These can be complemented with other appropriate markers as per local guidelines. Patients with active hepatitis B disease should not be treated with Rituximab. 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. The majority of patients had received Rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant.

Immunizations

The safety of immunization with live viral vaccines, following Rituximab therapy has not been studied for NHL patients and vaccination with live virus vaccines is not recommended. Patients treated with Rituximab may receive non-live vaccinations. However with non-live vaccines response rates may be reduced.

Mean pre-therapeutic antibody titers against a panel of antigens (Streptococcus pneumonia, 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 Rituximab, treatment should be permanently discontinued.

Concomitant/sequential use of other DMARDs in rheumatoid arthritis

The concomitant use of Rituximab and anti-rheumatic therapies other than those specified under the rheumatoid arthritis indication and posology is not recommended.

There are limited data from clinical trials to fully assess the safety of the sequential use of other DMARDs (including TNF inhibitors and other biologics) following Rituximab. The available data indicate that the rate of clinically relevant infection is unchanged when such therapies are used in patients previously treated with Rituximab, however patients should be closely observed for signs of infection if biologic agents and/or DMARDs are used following Rituximab therapy.

Malignancy

Immunomodulatory drugs may increase the risk of malignancy. On the basis of limited experience with Rituximab in rheumatoid arthritis patients 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.

4.5 Interaction with other medicinal products and other forms of interaction

In patients with CLL, Rituximab did not alter systemic exposure to fludarabine or cyclophosphamide. In clinical trials of patients with RA, concomitant administration of methotrexate or cyclophosphamide did not alter the pharmacokinetics of rituximab.

4.6 Usage in special populations

Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of Rituximab in pregnant women. Women of childbearing potential should use effective contraception while receiving Rituximab and for 12 months following treatment. Rituximab should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Human data

Post-marketing data indicate that B-cell lymphocytopenia generally lasting less than six months can occur in infants exposed to Rituximab in-utero. Rituximab was detected postnatally in the serum of infants exposed in-utero.

Animal data

In an embryo-fetal developmental toxicity study performed on pregnant cynomolgus monkeys, Rituximab crosses the monkey placenta. Exposed offspring did not exhibit any teratogenic effects but did have decreased lymphoid tissue B cells. Decreased B cells and immunosuppression were noted in the offspring of Rituximab treated pregnant animals in subsequent pre-and postnatal reproductive toxicity studies and the B-cell counts returned to normal levels, and immunologic function was restored within 6 months postpartum.

Nursing Mothers

It is not known whether Rituximab is secreted into human milk. However, Rituximab is secreted in the milk of lactating cynomolgus monkeys, and IgG is secreted in human milk. Published data suggest that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts. The unknown risks to the infant from oral ingestion of Rituximab should be weighed against the known benefits of breastfeeding.

Paediatric Use

The safety and effectiveness of Rituximab in pediatric patients have not been established.

Geriatric Use

Diffuse Large B-Cell NHL

In clinical studies conducted in patients with DLBCL, no overall differences in effectiveness were observed between patients and younger patients. Cardiac adverse reactions, mostly supraventricular arrhythmias, occurred more frequently among elderly patients. Serious pulmonary adverse reactions were also more common among the elderly, including pneumonia and pneumonitis.

Low-Grade or Follicular Non-Hodgkin's Lymphoma

In a clinical study conducted in patients with previously untreated follicular NHL, no overall differences in safety or effectiveness were observed between patients and younger patients.

Rheumatoid Arthritis

In clinical studies conducted in patients with RA, the incidences of adverse reactions were similar between older and younger patients. The rates of serious adverse reactions, including serious infections, malignancies, and cardiovascular events were higher in older patients.

No differences in safety or efficacy were observed between younger and older patients. No dose adjustment is required on the basis of patient age.

Granulomatosis with Polyangiitis (GPA) and Microscopic Polyangiitis (MPA)

In clinical studies conducted in patients with GPA and MPA, there is no overall differences in efficacy were observed between patients that were 65 years old and over and younger patients. The overall incidence and rate of all serious adverse events was higher in patients 65 years old and over.

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, although the 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’s lymphoma and chronic lymphocytic leukaemia

The following safety profile of Rituximab in non-Hodgkin's lymphoma is based on data 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 common adverse reactions of Rituximab (incidence ≥ 25%) observed in clinical trials of patients with NHL were infusion reactions, fever, lymphopenia, chills, infection, and asthenia occurred in the majority of patients during the first infusion. The incidence of infusion-related symptoms decreases substantially with subsequent infusions and is less than 1% after eight doses of Rituximab.

Infectious events (predominantly bacterial and viral) occurred in approximately 30-55% of patients during clinical trials in patients with NHL.
The most frequent reported or observed serious adverse drug reactions were:

- IRRs (including cytokine-release syndrome, tumour-lysis syndrome)
- Infections
- Cardiovascular events
- Other serious ADRs reported include hepatitis B reactivation and PML

Infusion Reactions

Signs and symptoms suggestive of an infusion-related reaction were reported in more than 50% of patients in clinical trials, and were predominantly seen during the first infusion, usually in the first one to two hours. These symptoms mainly comprised fever, chills and rigors. Other symptoms included flushing, angioedema, bronchospasm, vomiting, nausea, urticaria/rash, myalgia, dizziness, fatigue, headache, throat irritation, rhinitis, pruritus, pain, tachycardia, hypertension, hypotension, dyspnoea, dyspepsia, asthenia and features of tumor lysis syndrome. Severe infusion-related reactions (such as bronchospasm, hypotension) occurred in up to 12% of the cases. Additional reactions reported in some cases were myocardial infarction, atrial fibrillation, 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 and atrial fibrillation), pulmonary oedema, multi-organ failure, tumor lysis syndrome, cytokine release syndrome, renal failure, and respiratory failure were reported at lower or unknown frequencies. The incidence of infusion-related symptoms decreased substantially with subsequent infusions and is < 1% of patients by the eighth cycle of Rituximab (-containing) treatment.

Infections

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

Localized candida infections as well as Herpes zoster was reported at a higher incidence in the Rituximab-containing arm of randomized studies. Severe infections were reported in about 4% of patients treated with Rituximab monotherapy. Higher frequencies of infections overall, including grade 3 or 4 infections, were observed during Rituximab maintenance treatment up to 2 years when compared to observation. There was no cumulative toxicity in terms of infections reported over a 2-year treatment period. In addition, other serious viral infections either new, reactivated or exacerbated, some of which were fatal, have been reported with Rituximab treatment. The majority of patients

had received Rituximab in combination with chemotherapy or as part of a 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. 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. Rarely Pneumo-cystis jirovecii have been reported.

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. 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. 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 studies of Rituximab in patients with Waldenstrom's macroglobulinaemia, transient increases in serum IgM levels have been observed following treatment initiation, which may be associated with hyperviscosity and related symptoms. The transient IgM increase usually returned to at least baseline level within 4 months.

Cardiovascular 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.

Respiratory system

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

Neurologic events

During the treatment period, 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.

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’s lymphoma. In the majority of these cases, Rituximab was administered with chemotherapy.

IgG levels

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

remained constant in the Rituximab group. The proportion of patients with IgG levels below the LLN was about 60% in the Rituximab group throughout the 2 year treatment period, while it decreased in the observation group (36% after 2 years).

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.

The other adverse reactions which have been reported with Rituximab were Febrile infections, depression, nervousness, paraesthesia, hypoaesthesia,agitation, insomnia, vasodilatation, anxiety, Dysgeusia, peripheral neuropathy, facial nerve palsy, cranial neuropathy, loss of other senses, lacrimation disorder, lacrimation disorder, conjunctivitis, severe vision loss, tinnitus, ear pain, hearing loss, febrile neutropenia, granulo-cytopenia, peripheral oedema, face oedema, increased LDH, hypo-calcaemia, orthostatic hypotension, leuko-cytoclastic vasculitis, increased cough, chest pain, respiratory disease, asthma, hypoxia, lung infiltration, diarrhoea, abdominal pain, dysphagia, stomatitis, constipation, anorexia, abdominal enlargement, alopecia, sweating, night sweats, skin disorder, severe bullous skin reactions, hypertonia, arthralgia, back pain, neck pain, tumour pain, malaise, cold syndrome and shivering.

Post-marketing Experience
The following reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to Rituximab.

Hematologic
Prolonged pancytopenia, marrow hypoplasia, Grade 3-4 prolonged or late-onset neutropenia, hyper viscosity syndrome in Waldenstrom’s macroglobulinemia and prolonged hypo gammaglobulinemia.

Cardiac: Fatal cardiac failure
Immune/Autoimmune Events: Uveitis, optic neuritis, systemic vasculitis, pleuritis, lupus-like syndrome, serum sickness, polyarticular arthritis and vasculitis with rash

Infection: Viral infections, including progressive multifocal leukoencephalopathy (PML), increase in fatal infections in HIV-associated lymphoma and a reported increased incidence of Grade 3 and 4 infections.
Neoplasia: Disease progression of Kaposi's sarcoma
Skin: Severe mucocutaneous reactions
Gastrointestinal: Bowel obstruction and perforation
Pulmonary: Fatal bronchiolitis obliterans and fatal interstitial lung disease.
Nervous system: Posterior Reversible Encephalopathy Syndrome (PRES) / Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

Experience from rheumatoid arthritis

The overall safety profile of Rituximab in rheumatoid arthritis is based on data from patients from clinical trials and from post-marketing surveillance. The most frequent adverse reactions considered due to receipt of Rituximab were IRRs. The overall incidence of IRRs in clinical trials was 23% with the first infusion and decreased with subsequent infusions. Serious IRRs were uncommon (0.5% of patients) and were predominantly seen during the initial course. In addition to adverse reactions seen in RA clinical trials for Rituximab, progressive multifocal leukoencephalopathy (PML) and serum sickness-like reaction have been reported during post marketing experience.

Table 1: 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 effects
Infections and Infestations	Upper respiratory tract infection, urinary tract infections, bronchitis, sinusitis, gastroenteritis, tinea pedis, PML and reactivation of hepatitis B
Blood and lymphatic system disorders	Neutropenia, late neutropenia and serum sickness-like reaction
Cardiac Disorders	Angina pectoris, atrial fibrillation, heart failure, myocardial infarction and atrial flutter
Immune System Disorders	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	Infusion related reactions (generalized oedema,

	bronchospasm, wheezing, laryngeal oedema, angioneurotic oedema, generalized pruritus, anaphylaxis, anaphylactoid reaction)
Metabolism and Nutritional Disorders	Hypercholesterolemia
Nervous System disorders	Headache, paraesthesia, migraine, dizziness and sciatica
Skin and Subcutaneous Tissue Disorders	Alopecia, Toxic Epidermal Necrolysis (Lyell's syndrome) and stevens-Johnson syndrome
Psychiatric Disorders	Depression and anxiety
Gastrointestinal Disorders	Dyspepsia, diarrhoea, gastro-oesophageal reflux, mouth ulceration and upper abdominal pain
Musculo skeletal disorders	Arthralgia / musculoskeletal pain, osteoarthritis and bursitis
Investigations	Decreased IgM levels and decreased IgG levels

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.

Infusion-related reactions

The most frequent ADRs following receipt of Rituximab in clinical studies were IRRs. The incidence of IRRs declined with subsequent infusions. Premedication with intravenous glucocorticoid significantly reduced the incidence and severity of IRRs. Severe IRRs with fatal outcome have been reported in the post-marketing setting.

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. 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.

Experience from granulomatosis with polyangiitis and microscopic polyangiitis

The following safety profile of Rituximab in granulomatosis with polyangiitis and microscopic polyangiitis is based on data from clinical trials and post marketing surveillance.

Blood and lymphatic system disorders: Thrombocytopenia

Gastrointestinal disorders: Diarrhea, dyspepsia, constipation

General disorders and administration site conditions: Peripheral edema

Immune system disorders: Cytokine release syndrome

Infections and infestations: Urinary tract infection, bronchitis, herpes zoster, nasopharyngitis

Investigations: Decreased hemoglobin

Metabolism and nutrition disorders: Hyperkalemia

Musculoskeletal and connective tissue disorders: Muscle spasms, arthralgia, back pain, muscle weakness, musculoskeletal pain, pain in extremities

Nervous system disorders: Dizziness, tremor

Psychiatric disorders: Insomnia

Respiratory, thoracic and mediastinal disorders: Cough, dyspnea, epistaxis, nasal congestion

Skin and subcutaneous tissue disorders: Acne

Vascular disorders: Hypertension, flushing

Infusion-related reactions

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 was pneumonia.

Cardiovascular adverse reactions

The most frequently reported adverse events were tachycardia and atrial fibrillation.

Hypogammaglobulinaemia

Hypogammaglobulinemia (IgA, IgG or IgM below the lower limit of normal) has been observed in patients with GPA and MPA treated with Rituximab.

4.9 Overdose

There has been no experience of over dosage with Rituximab. Patients who experience overdose should have immediate interruption of their infusion and be closely monitored.

5.0 Pharmacological Properties

5.1 Pharmacodynamics properties

Mechanism of Action

Rituximab is a monoclonal antibody that targets the CD20 antigen expressed on the surface of pre-B and mature B-lymphocytes. Upon binding to CD20, Rituximab mediates B-cell lysis. Possible mechanisms of cell lysis include complement dependent cytotoxicity (CDC) and antibody dependent cell mediated cytotoxicity (ADCC). The antibody induced apoptosis in the DHL 4 human B cell lymphoma cell line.

B cells are believed to play a role in the pathogenesis of rheumatoid arthritis (RA) and associated chronic synovitis. In this setting, B cells may be acting at multiple sites in the autoimmune/inflammatory process, including through production of rheumatoid factor (RF) and other autoantibodies, antigen presentation, T-cell activation, and/or proinflammatory cytokine production.

Pharmacodynamics

CD20 is found on both normal and malignant B cells, but not on hematopoietic stem cells, pro-B cells, normal plasma cells or other normal tissue. This antigen does not internalize 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.

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

CD20 antigen on B lymphocytes has also been demonstrated to induce cell death via apoptosis.

Immunogenicity

There is a potential for immunogenicity with Rituximab like all therapeutic proteins. The observed incidence of antibody (including neutralizing antibody) positivity in an assay is highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Rituximab with the incidence of antibodies to other products may be misleading.

5.2 Pharmacokinetic properties

Non-Hodgkin's Lymphoma (NHL)

Pharmacokinetics was characterized in 203 NHL patients receiving 375 mg/m^2 Rituximab weekly by intravenous infusion for 4 doses. Rituximab was detectable in the serum of patients 3 to 6 months after completion of treatment.

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.

Based on a population pharmacokinetic analysis of data from 298 NHL patients who received Rituximab once weekly or once every three weeks, the estimated median terminal elimination half-life was 22 days (range, 6.1 to 52 days). Patients with higher CD19-positive cell counts or larger measurable tumor lesions at pretreatment had a higher clearance. However, dose adjustment for pretreatment CD19 count or size of tumor lesion is not necessary. Age and gender had no effect on the pharmacokinetics of Rituximab.

Rheumatoid Arthritis

Following administration of 2 doses of Rituximab in patients with RA, the mean (±S.D.; % CV) concentrations after the first infusion (Cmax first) and second infusion (Cmax second) were 157 (±46; 29%) and 183 (±55; 30%) mcg/mL, and 318 (± 86; 27%) and 381 (± 98; 26%) mcg/mL for the 2 x 500 mg and 2 x 1000 mg doses, respectively.

Based on a population pharmacokinetic analysis of data from 2005 RA patients who received Rituximab, the estimated clearance of rituximab was 0.335 L/day; volume of distribution was 3.1 L and mean terminal elimination half-life was 18.0 days (range, 5.17 to 77.5 days). Age, weight and gender had no effect on the pharmacokinetics of rituximab in RA patients.

Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis

Based on the population pharmacokinetic analysis of data from GPA and MPA patients who received 375 mg/m2 rituximab once weekly by intravenous infusion for four weeks, the estimated median terminal elimination half-life was 23 days (range, 9 to 49 days). Rituximab mean clearance and volume of distribution were 0. 312 L/day (range, 0.115 to 0.728 L/day) and 4.50 L (range, 2.21 to 7.52 L) respectively.

5.3 Preclinical safety data

In single dose toxicity studies with Rituximab in rats and mice, no clinical signs of toxicity and mortality were observed at doses of 516.6mg/kg body weight and 512.5mg/kg body weight respectively. In repeated dose toxicity studies with Rituximab in rats and rabbits, the no observed adverse effect level (NOAEL) were observed at doses of 258.3mg/kg body weight and 129.2mg/kg body weight respectively. In guinea pigs, Rituximab was observed to have no skin sensitization potential. Rituximab was found to be non-irritant to the skin of rabbits. No toxicologically significant effect on the immunological parameters of male and female rats at 51.7 mg/kg body weight was observed. These observations were observed with studies involving in-house Rituximab product.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term animal studies have been performed to establish the carcinogenic or mutagenic potential of Rituximab or to determine potential effects on fertility in males or females.

Reproductive Toxicology Studies: An embryo-fetal developmental toxicity study was performed on pregnant cynomolgus monkeys. Rituximab crosses the monkey placenta. Exposed offspring did not exhibit any teratogenic effects but did have decreased lymphoid tissue B cells.

A subsequent pre- and postnatal reproductive toxicity study in cynomolgus monkeys was completed to assess developmental effects including the recovery of B cells and immune function in infants exposed to rituximab in utero. Regardless of the timing of treatment, decreased B cells and immunosuppression were noted in the offspring of rituximab-treated pregnant animals. The B-cell counts returned to normal levels, and immunologic function was restored within 6 months postpartum.

6.0 Pharmaceutical Particulars

6.1 List of excipients

S. No.	Ingredients	Function
1	Tri sodium citrate dihydrate	Buffering agent
2	Sodium chloride	Tonicity Agent
3	Polysorbate 80	Stabilizer
4	Water for Injection	Solvent

6.2 Incompatibilities

Do not administer Rituximab injection in conjunction with other drug solutions.

6.3 Shelf life

30 Months.

The prepared infusion solution of Rituximab is physically and chemically stable for 24 hours at 2˚C – 8˚C and subsequently 12 hours at room temperature.

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

6.4 Special precautions for storage

Should be store in a refrigerator at 2˚C to 8˚C. Keep the container in the outer carton in order to protect from light.

6.5 Nature and contents of container

The following presentations are available:

S. No.	Strengths / Dosages
1.	**Rituximab Injection: 100 mg** Rituximab Injection 10 ml single dose vial Each 10 ml contains 100 mg of Rituximab (10mg/ml).
2.	**Rituximab Injection: 500 mg** Rituximab Injection 50 ml single dose vial Each 50 ml contains 500 mg of Rituximab (10mg/ml).

Container closure system is the primary packaging item of the Rituximab drug product. 10 ml and 50 ml clear glass vial: neutral (USP Type 1) with butyl rubber stopper is used to fill

Rituximab drug product. The rubber stopper is formulated with elastomer butyl coated with FluroTec®. Upon filling of the drug product into the glass vial, the vial is stoppered with an elastomeric butyl rubber stopper and sealed with flip-off seal.

6.6 Special precautions for disposal

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

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

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

7.0 Marketing Authorisation / Prequalification Holder

Manufactured by:

Hetero Biopharma Limited,
Sy. No. 458 (Part), TSIIC-Formulation SEZ,
Polepally (Village), Jadcherla (Mandal)
Mahaboobnagar (District) – 509 301,
Telangana, India.

8.0 Marketing Authorization Number(s)

05499/07342/NMR/2019
05516/07347/NMR/2019

9.0 Date of first authorisation / renewal of the authorisation

Date of first authorisation: Nov 20, 2020 and Nov 27, 2020