SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Rituximab 500 mg / 50 mL (10 mg / mL) concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains 10 mg of rituximab.
Each 50 ml single-use vial contains 500 mg of rituximab.

Rituximab is a genetically engineered chimeric mouse/human monoclonal antibody representing a glycosylated immunoglobulin with human IgG1 constant regions and murine light-chain and heavy-chain variable region sequences. The antibody is produced by mammalian (Chinese hamster ovary) cell suspension culture
For a full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion. Sterile, clear and colourless liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Non-Hodgkin's lymphoma (NHL)
Rituximab is indicated for the treatment of previously untreated patients with stage III - IV follicular lymphoma in combination with chemotherapy.

Rituximab maintenance therapy is indicated for patients with relapsed/refractory follicular lymphoma responding to induction therapy with chemotherapy with or without Rituximab.

Rituximab monotherapy is indicated for treatment of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy.

Rituximab is indicated for the treatment of patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy.

Chronic lymphocytic leukaemia (CLL)

Rituximab is indicated for first-line treatment of patients with chronic lymphocytic leukaemia (CLL) in combination with chemotherapy. Only limited data are available on efficacy and safety for patients previously treated with monoclonal antibodies including rituximab or patients refractory to previous rituximab plus chemotherapy.

Rheumatoid arthritis

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

4.2 Posology and Method Of Administration

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

Posology

Non-Hodgkin's lymphoma

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.

Follicular non-Hodgkin's lymphoma

Combination therapy

The recommended dose of rituximab 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 up to 8 cycles.

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

Monotherapy/Maintenance Therapy

Previously untreated follicular lymphoma

The recommended dose of rituximab used as a maintenance treatment for patients with previously untreated follicular

lymphoma who have responded to induction treatment is: 375 mg/m^2 body surface area once every 2 months (starting 2 months after the last dose of induction therapy) until disease progression or for a maximum period of two years.

Relapsed/refractory follicular lymphoma
The recommended dose of rituximab used as a maintenance treatment for patients with relapsed/refractory follicular lymphoma who have responded to induction treatment is: 375 mg/m2 body surface area once every 3 months (starting 3 months after the last dose of induction therapy) until disease progression or for a maximum period of two years.

The recommended dose of rituximab monotherapy used as induction treatment for adult patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy is: 375 mg/m^2 body surface area, administered as an intravenous infusion once weekly for four weeks.

For retreatment with rituximab monotherapy for patients who have responded to previous treatment with rituximab monotherapy for relapsed/refractory follicular NHL, the recommended dose is: 375 mg/m^2 body surface area, administered as an intravenous infusion once weekly for four weeks.

Diffuse large B cell non-Hodgkin's lymphoma

Rituximab should be used in combination with CHOP chemotherapy. The recommended dosage is 375 mg/m^2 body surface area, administered on day 1 of each chemotherapy cycle for 8 cycles after intravenous infusion of the glucocorticoid component of CHOP. Safety and efficacy of rituximab have not been established in combination with other chemotherapies in diffuse large B cell non-Hodgkin’s lymphoma.

Chronic lymphocytic leukaemia

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

The recommended dosage of rituximab 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 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 infusion.

Rheumatoid arthritis

Patients should receive treatment with 100 mg intravenous methylprednisolone to be completed 30 minutes prior to rituximab infusions to decrease the incidence and severity of infusion related reactions. Premedication consisting of an analgesic/anti-pyretic (e.g. paracetamol) and an antihistaminic drug (e.g. diphenhydramine) should always be administered before each infusion of rituximab.

A course of rituximab consists of two 1000 mg intravenous infusions. The recommended dosage of rituximab is 1000 mg by intravenous infusion followed by a second 1000 mg intravenous infusion two weeks later.

Disease activity should be regularly monitored. There are limited clinical data on the safety and efficacy of further courses of therapy with rituximab.

Human anti chimeric antibodies (HACA) develop in some patients after the first course of rituximab. The presence of HACA may be associated with the worsening of infusion or allergic reactions after the second infusion of subsequent courses. Furthermore, in one case with HACA, failure to deplete B-cells after receipt of further treatment courses has been observed. Thus, the benefit/risk balance of therapy with rituximab should be carefully considered before administering subsequent courses of rituximab. If a repeat course of treatment is considered it should not be given at an interval less than 16 weeks.

Background therapy with glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs, or analgesics can be continued during treatment with rituximab.

Rheumatoid arthritis patients should receive treatment with 100 mg intravenous methylprednisolone 30 minutes prior to rituximab to decrease the rate and severity of acute infusion reactions.

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.

Special populations

Paediatric population
The safety and efficacy of rituximab in children has not been established.

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

Method of Administration

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

In Rheumatoid Arthritis, premedication with glucocorticoids should also be administered in order to reduce the frequency and severity of infusion-related reactions.

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

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

Subsequent infusions: Subsequent doses of 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.

The prepared rituximab solution should be administered as an intravenous infusion through a dedicated i.v. line. It should not be administered as an intravenous push or bolus.

Patients should be closely monitored for the onset of cytokine release syndrome. Patients who develop evidence of severe reactions, especially severe dyspnoea, bronchospasm or hypoxia

should have the infusion interrupted immediately. Patients with non-Hodgkin's lymphoma should then be evaluated for evidence of tumour lysis syndrome including appropriate laboratory tests and, for pulmonary infiltration, with a chest x-ray. In all patients, the infusion should not be restarted until complete resolution of all symptoms, and normalisation of laboratory values and chest x-ray findings. At this time, the infusion can be initially resumed at not more than one-half the previous rate. If the same severe adverse reactions occur for a second time, the decision to stop the treatment should be seriously considered on a case by case basis.

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

4.3 Contraindications

Contraindications for use in non-Hodgkin's lymphoma and chronic lymphocytic leukaemia

Hypersensitivity to the active substance or to any of the excipients Active, severe infections
Patients in a severely immunocompromised state

Contraindications for use in rheumatoid arthritis

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

4.4 Special Warnings And Precautions For Use

- **Progressive Multifocal Leukoencephalopathy**

Use of Rituximab may be associated with an increased risk of Progressive Multifocal Leukoencephalopathy (PML). Patients must be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML. If PML is suspected, further dosing must be suspended until PML has been excluded. The clinician should evaluate the patient to determine if the symptoms are indicative of neurological dysfunction, and if so, whether these symptoms are possibly suggestive of PML. Consultation with a Neurologist should be considered as clinically indicated.

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

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

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

- **<u>Non-Hogkin's lymphoma and chronic lymphocytic leukaemia</u>**
- Infusion reactions

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

Severe cytokine release syndrome is characterised by severe dyspnea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. This syndrome may be associated with some features of ***tumour lysis syndrome*** such as hyperuricaemia, hyperkalaemia, hypocalcaemia, hyperphosphaetemia, acute renal failure, elevated Lactate dehydrogenase (LDH) and may be associated with acute respiratory failure and death. The acute respiratory failure may be accompanied by events such as pulmonary interstitial infiltration or oedema, visible on a chest x-ray. The syndrome frequently manifests itself within one or two hours of initiating the first infusion. Patients with a history of pulmonary insufficiency or those with pulmonary tumour infiltration may be at greater risk of poor outcome and should be treated with increased caution. Patients who develop severe cytokine release syndrome should have their infusion interrupted immediately and should receive aggressive symptomatic treatment. Since initial improvement of clinical symptoms may be followed by deterioration, these patients should be closely monitored until tumour lysis syndrome and pulmonary infiltration have been resolved or ruled out. Further

treatment of patients after complete resolution of signs and symptoms has rarely resulted in repeated severe cytokine release syndrome.

Infusion related adverse reactions including cytokine release syndrome accompanied by hypotension and bronchospasm have been observed in 10 % of patients treated with Rituximab. 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 glucocorticooids, 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 oedema and acute reversible thrombocytopenia.

Since hypotension may occur during rituximab infusion, consideration should be given to withholding anti-hypertensive medicines 12 hours prior to the rituximab infusion.

Cardiac disorders
Angina pectoris or cardiac arrhythmias such as atrial flutter and fibrillation, heart failure 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 10 /l and/or platelet counts < 75 x 10 /l as clinical experience

in this population is
limited. rituximab has been used in 21 patients who underwent autologous bone marrow transplantation and other risk groups with a presumable reduced bone marrow function without inducing myelotoxicity.

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

Infections:

Serious infections, including fatalities, can occur during therapy with rituximab. rituximab should not be administered to patients with an active and/or severe infection eg. tuberculosis, sepsis and opportunistic infections. Very rare cases of hepatitis B reactivation have been reported in subject receiving rituximab including fulminant hepatitis with fatal outcome.

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. Limited information from one study in relapsed/refractory CLL patients suggests that rituximab treatment may also worsen the outcome of primary hepatitis B infections. Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with 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 and CLL. 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 and CLL 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 pneumoniae, influenza A, mumps, rubella, 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, treatment should be permanently discontinued.

- **Rheumatoid arthritis**

Methotrexate (MTX) naïve populations with Rheumatoid arthritis
The use of rituximab is not recommended in MTX-naïve patients since a favourable benefit risk relationship has not been established.

Infusion related reactions
rituximab is associated with infusion related reactions (IRR), which may be related to release of cytokines and/or other chemical mediators. Premedication consisting of an analgesic/anti-pyretic drug and an anti-histaminic drug, should always be administered before each infusion of rituximab. In Rheumatoid arthritis premedication with glucocorticoids should also be administered before each infusion of rituximab in order to reduce the frequency and severity of infusion-related reactions.
Severe infusion-related reactions 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 infusion-related reaction 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.

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.

There are no data on the safety of rituximab in patients with moderate heart failure (NYHA class III) or severe, uncontrolled cardiovascular disease. In patients treated with rituximab, the occurrence of pre-existing ischemic cardiac conditions becoming symptomatic, such as angina pectoris, has been observed, as well as atrial fibrillation and flutter. Therefore, in patients with a known cardiac history, and those who experienced prior cardiopulmonary adverse reactions, the risk of cardiovascular complications resulting from infusion reactions should be considered before treatment with rituximab and patients closely monitored during administration. Since hypotension may occur during rituximab infusion,

consideration should be given to withholding anti-hypertensive medications 12 hours prior to the rituximab infusion.

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

Infections
Based on the mechanism of action of rituximab and the knowledge that B cells play an important role in maintaining normal immune response, patients have an increased risk of infection following rituximab therapy. 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) or severely immunocompromised patients (e.g. where levels of CD4 or CD8 are very low). Physicians should exercise caution when considering the use of rituximab in patients with a history of recurring or chronic infections or with underlying conditions which may further

predispose patients to serious infection, e.g. hypogammaglobulinaemia. It is recommended that immunoglobulin levels are determined prior to initiating treatment with rituximab.

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

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

Hepatitis B Infections
Cases of hepatitis B reactivation, including those with a fatal outcome, have been reported in Rheumatoid Arthritis, Granulomatosis with polyangiitis and Microscopic polyangiitis patients receiving rituximab.

Hepatitis B virus (HBV) screening should be performed in all patients 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.

Late neutropenia
Measure blood neutrophils prior to each course of rituximab, and regularly up to 6-months after cessation of treatment, and upon signs or symptoms of infection

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, treatment should be permanently discontinued.

Immunization

Physicians should review the patient's vaccination status and follow current immunization guidelines prior to rituximab therapy. Vaccination should be completed at least 4 weeks prior to first administration of rituximab.

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

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

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

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

Currently, there are limited data on possible drug interactions with

rituximab.
In CLL patients, co-administration with rituximab did not appear to have an effect on the pharmacokinetics of fludarabine or cyclophosphamide. In addition, there was no apparent effect of fludarabine and cyclophosphamide on the pharmacokinetics of rituximab.
Co-administration with methotrexate had no effect on the pharmacokinetics of rituximab in rheumatoid arthritis patients.
Patients with human anti-mouse antibody or human anti-chimeric antibody (HAMA/HACA) titres may have allergic or hypersensitivity reactions when treated with other diagnostic or therapeutic monoclonal antibodies. In patients with rheumatoid arthritis, 283 patients received subsequent therapy with a biologic DMARD following rituximab. In these patients the rate of clinically relevant infection while on rituximab was 6.01 per 100 patient years compared to 4.97 per 100 patient years following treatment with the biologic DMARD.

4.6 Pregnancy and lactation

Pregnancy:

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

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

Lactation:

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

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 events reported to date do not indicate that

such an effect is likely.

4.8 Undesirable effects

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

The most frequently observed adverse drug reactions (ADRs) in patients receiving rituximab were infusion-related reactions which occurred in the majority of patients during the first infusion. The incidence of infusion-related symptoms decreases substantially with subsequent infusions and is less than 1% after eight doses of rituximab.Infectious events (predominantly bacterial and viral) occurred in approximately 30-55 % of patients during clinical trials in patients with NHL and in 30-50 % of patients during clinical trials in patients with CLL.
The most frequent reported or observed serious adverse drug reactions were infusion related reactions (including cytokine-release syndrome, tumour-lysis syndrome), infections and cardiovascular events.
Other serious ADRs reported include hepatitis B reactivation and PML.
The frequencies of ADRs reported with rituximab alone or in combination with chemotherapy are summarised in Table 1. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1000) and very rare (< 1/10,000). The ADRs identified only during post-marketing surveillance, and for which a frequency could not be estimated, are listed under “not known”.

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

System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not known
Infections and infestations	bacterial infections, viral infections, bronchitis	sepsis, pneumonia, febrile infection, herpes zoster, respiratory tract		serious viral infection Pneumocysti s jirovecii	PML	

		infection, fungal				

		infections, infections of unknown aetiology, acute bronchitis, sinusitis, hepatitis B				
Blood and lymphatic system disorders	neutropenia, leucopenia, febrile neutropenia, thrombo-cytopenia	anaemia, pancytopenia, granulo-cytopenia	coagulation disorders, aplastic anaemia, haemolytic anaemia, lymph-adenopathy		transient increase in serum IgM levels	late neutropenia
Immune system disorders	infusion related reactions, angioedema	hypersensitivity		anaphylaxis	tumour lysis syndrome, cytokine release syndrome, serum sickness	infusion-related acute reversible thrombo-cytopenia
Metabolism and nutrition disorders		hyperglycaemia, weight decrease, peripheral oedema, face oedema, increased LDH, hypocalcaemia				
Psychiatric disorders			depression, nervousness,			

Nervous system disorders		paraesthesia, hypoaesthesia, agitation, insomnia, vasodilatation, dizziness, anxiety	dysgeusia		peripheral neuropathy, facial nerve palsy	cranial neuropathy, loss of other senses
Eye disorders		lacrimation disorder, conjunctivitis			severe vision loss	
Ear and labyrinth disorders		tinnitus, ear pain				hearing loss
Cardiac disorders		myocardial infarction , arrhythmia, atrial fibrillation, tachycardia , cardiac disorder	left ventricular failure, supra-ventricular tachycardia, ventricular tachycardia, angina, myocardial ischaemia, bradycardia	severe cardiac events	heart failure	
Vascular disorders		hypertension, orthostatic hypotension, hypotension			vasculitis (predominat ely cutaneous),	

					leukocytoclastic vasculitis	
Respiratory, thoracic and mediastinal disorders		Bronchospasm, respiratory disease, chest pain, dyspnoea, increased cough, rhinitis	asthma, bronchiolitis obliterans, lung disorder, hypoxia	interstitial lung disease	respiratory failure,	lung infiltration,
Gastrointestinal disorders	nausea	vomiting, diarrhoea, abdominal pain, dysphagia, stomatitis, constipation, dyspepsia, anorexia, throat irritation	abdominal enlargement		gastro-intestinal perforation	
Skin and subcutaneous tissue disorders	pruritus, rash, alopecia	urticaria, sweating, night sweats, skin disorder			severe bullous skin reactions, Stevens-Johnson Syndrome toxic epidermal necrolysis (Lyell's Syndrome)	
Musculoskeletal, connective tissue and bone disorders		hypertonia, myalgia, arthralgia, back pain, neck pain, pain				
Renal and urinary disorders					renal failure	

General disorders and administration site conditions	fever, chills, asthenia, headache	tumour pain, flushing, malaise, cold syndrome, fatigue, shivering, multi-organ failure	infusion site pain			
Investigations	decreased IgG levels					

Experience from rheumatoid arthritis

The most frequent adverse reactions considered due to receipt of rituximab were infusion related reactions. 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.

Events are listed in Table 2. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), and very rare (<1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 2 Summary of adverse drug reactions reported in clinical trials or during postmarketing surveillance occurring in patients with rheumatoid arthritis receiving rituximab

System Organ Class	Very Common	Common	Uncommon	Rare	Very rare
Infections and Infestations	upper respiratory tract infection, urinary tract infections	Bronchitis, sinusitis, gastroenteritis, tinea pedis			PML, reactivation of hepatitis B
Blood and lymphatic system disorders		neutropenia		late neutropenia	Serum sickness-like reaction
Cardiac Disorders				Angina pectoris, atrial fibrillation, heart	Atrial flutter

				failure, myocardial infarction	
Immune System Disorders **General disorders and administration site conditions**	Infusion related reactions (hypertension, nausea, rash, pyrexia, pruritus, urticaria, throat irritation, hot flush, hypotension, rhinitis, rigors, tachycardia, fatigue, oropharyngeal pain, peripheral oedema, erythema)		Infusion related reactions (generalized oedema, bronchospasm, wheezing, laryngeal oedema, angioneurotic oedema, generalized pruritis, anaphylaxis, anaphylactoid reaction)		
Metabolism and Nutritional Disorders		hyper-cholesterolemia			
Nervous System disorders	headache	paraesthesia, migraine, dizziness, sciatica			
Skin and Subcutaneous Tissue Disorders		alopecia			Toxic Epidermal Necrolysis (Lyell's Syndrome), Stevens-Johnson Syndrome
Psychiatric Disorders		depression, anxiety			

Gastrointestinal Disorders		Dyspepsia, diarrhoea, gastro-oesophageal reflux, mouth ulceration, upper abdominal pain			
Musculoskeletal disorders		arthralgia / musculoskeletal pain, osteoarthritis, bursitis			
Investigations	decreased IgM levels	decreased IgG levels			

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via the relevant national regulatory authority pharmacovigilance.

4.9 Overdose

There has been no experience of overdose in human clinical trials. However, single doses higher than 1000 mg have not been tested in controlled clinical trials in patients with autoimmune disease. The highest dose tested to date is 5g in patients with chronic lymphocytic leukaemia. No additional safety signals were identified.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Rituximab binds specifically to the transmembrane antigen, CD20, a non-glycosylated phosphoprotein, located on pre-B and mature B lymphocytes. The antigen is expressed on >95 % of all B cell non-Hodgkin's lymphomas.

CD20 is found on both normal and malignant B cells, but not on haematopoietic stem cells, pro-B cells, normal plasma cells or

other normal tissue. This antigen does not internalise upon antibody binding and is not shed from the cell surface. CD20 does not circulate in the plasma as a free antigen and, thus, does not compete for antibody binding.

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. Possible mechanisms of effector-mediated cell lysis include complement-dependent cytotoxicity (CDC) resulting from C1q binding, and antibody-dependent cellular cytotoxicity (ADCC) med iated by on eo r more of the Fcγ receptors on the surface of granulocytes, macrophages and NK cells. Rituximab binding to CD 20 antigen on B lymphocytes has also been demonstrated to induce cell death via apoptosis.

Peripheral B cell counts declined below normal following completion of the first dose of rituximab. In patients treated for hematological malignancies, B cell repletion began within 6 months of treatment returning to normal levels between 9 and 12 months after completion of therapy.

In rheumatoid arthritis patients, immediate depletion of B cells in the peripheral blood was observed following two infusions of 1000 mg rituximab separated by a 14 day interval. Peripheral blood B cell counts begin to increase from week 24 and evidence for repopulation is observed in the majority of patients by week 40, whether rituximab was administered as monotherapy or in combination with methotrexate.

Clinical Experience in Non-Hodgkin lymphoma:

Results of four randomized trials using rituximab in combination with chemotherapy regimens like CVP, CHOP, MCP, CHVP/Interferon-α have also demonstrated significant improvements in response rates, time-dependent parameters as well as in overall survival. Key results from all the four studies are summarized in below mentioned table.

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

Study	Treatment, N	Median FU, months	ORR, %	CR, %	Median TTF/PFS/ EFS mo	OS rates, %

M39021	CVP, 159 R-CVP, 162	53	57 81	10 41	Median TTP: 14.7 33.6 P<0.0001	53-months 71.1 80.9 p=0.029
GLSG'00	CHOP, 205 R-CHOP, 223	18	90 96	17 20	Median TTF: 2.6 years Not reached p < 0.001	18-months 90 95 p = 0.016
OSHO-39	MCP, 96 R-MCP, 105	47	75 92	25 50	Median PFS: 28.8 Not reached p < 0.0001	48-months 74 87 p = 0.0096
FL2000	CHVP-IFN, 183 R-CHVP-IFN, 175	42	85 94	49 76	Median EFS: 36 Not reached p < 0.0001	42-months 84 91 p = 0.029

EFS – Event Free Survival; TTP – Time to progression or death; PFS – Progression-Free Survival TTF – Time to Treatment Failure; OS rates – survival rates at the time of the analyses
N- Number of subjects

Clinical experience in Chronic lymphocytic leukaemia :

Results of randomized controlled trials, comparing FC chemotherapy (fludarabine 25 mg/m2, cyclophosphamide 250 mg/m2, days 1-3) every 4 weeks for 6 cycles or rituximab in combination with FC (R-FC) in previously untreated patients of CLL and patients with relapsed/refractory CLL showed significant benefit of R-FC treatment over FC chemotherapy alone in terms of overall survival and progression free survival (PFS).

Table-4: First-line treatment of chronic lymphocytic leukaemia Overview of efficacy results for rituxmab plus FC vs. FC alone - 48.1 months median observation time

Efficacy Parameter	**Kaplan-Meier Estimate of Median Time to Event (Months)**			Risk Reduction
	FC (N = 409)	**R-FC (N=408)**	**Log-Rank p value**	
Progression-free survival (PFS)	32.8	55.3	<0.0001	45%
Overall Survival	NR	NR	0.0319	27%
Event Free Survival	31.3	51.8	<0.0001	44%
Response rate (CR, nPR, or PR) CR rates	72.6% 16.9%	85.8% 36.0%	<0.0001 <0.0001	n.a. n.a.

Duration of response*	36.2	57.3	<0.0001	44%
Disease free survival (DFS)**	48.9	60.3	0.0520	31%
Time to new treatment	47.2	69.7	<0.0001	42%
Progression-free survival (PFS)	32.8	55.3	<0.0001	45%
Response rate and CR rates analysed using Chi-squared Test. NR: not reached; n.a.: not applicable *: only applicable to patients achieving a CR, nPR, PR **: only applicable to patients achieving a CR				

Table-5: Treatment of relapsed/refractory chronic lymphocytic leukaemia - overview of efficacy results for rituximab plus FC vs. FC alone (25.3 months median observation time)

Efficacy Parameter	**Kaplan-Meier Estimate of Median Time to Event (Months)**			Risk Reduction
	FC (N = 409)	**R-FC (N=408)**	**Log-Rank p value**	
Progression-free survival (PFS)	20.6	30.6	0.0002	35%
Overall Survival	51.9	NR	0.2874	17%
Event Free Survival	19.3	28.7	0.0002	36%
Response rate (CR, nPR, or PR)	58.0%	69.9%	0.0034	n.a.
CR rates	13.0%	24.3%	0.0007	n.a.
Duration of response *	27.6	39.6	0.0252	31%
Disease free survival (DFS)**	42.2	39.6	0.8842	-6%
Time to new CLL treatment	34.2	NR	0.0024	35%
Response rate and CR rates analysed using Chi-squared Test. **: only applicable to patients achieving a CR, nPR, PR; NR: not reached n.a. not applicable* ***: only applicable to patients achieving a CR;*				

Clinical Experience in Rheumatoid Arthritis:

The efficacy and safety of rituximab in alleviating the symptoms and signs of rheumatoid arthritis was demonstrated in three randomized, controlled, double-blind, multicenter studies.

In all three studies, rituximab 2 x 1000 mg significantly increased the proportion of patients achieving at least a 20 % improvement in ACR score compared with patients treated with methotrexate alone (Table). The treatment effect was similar in patients independent of rheumatoid factor status, age, gender, body surface area, race, number of prior treatments or disease status.

Table 6. Cross-study Comparison of ACR Responses at Week 24

ACR Response	Placebo+MTX	Rituximab+MTX
Study 1	N= 201	N= 298
ACR20	36 (18%)	[1] 153 (51%)
ACR50	11 (5%)	[1] 80 (27%)
ACR70	3 (1%)	[1] 37 (12%)
Study 2	N= 143	N= 185
ACR20	45 (31%)	[2] 96 (52%)
ACR50	19 (13%)	[2] 61 (33%)
ACR70	6 (4%)	[2] 28 (15%)
Study 3	N= 40	N= 40
ACR20	15 (38%)	[3] 28 (70%)
ACR50	5 (13%)	[3] 17 (43%)
ACR70	2 (5%)	[3] 9 (23%)

[1] [2] [3]
p ≤ p ≤ p <0.05
0.0001; 0.001;

MTX – Methotrexate

Clinically and statistically significant improvement was also noted on all individual components of the ACR response (tender and swollen joint counts, patient and physician global assessment, disability index scores (HAQ), pain assessment and C-Reactive Proteins (mg/dL).

5.2 Pharmacokinetic properties

Non-Hodgkin's lymphoma

Based on a population pharmacokinetic analysis in 298 NHL patients who received single or multiple infusions of rituximab as a single agent or in combination with CHOP therapy (applied rituximab doses ranged from 100 to 500 mg/m^2), the typical population estimates of nonspecific clearance (CL_1), specific clearance (CL_2) likely contributed by B cells or tumor burden, and central compartment volume of distribution (V_1) were 0.14 L/day, 0.59 L/day, and 2.7 L, respectively. Age, gender and WHO performance status had no effect on the pharmacokinetics of rituximab. This analysis suggests that dose adjustment of rituximab with any of the tested covariates is not expected to result in a meaningful reduction in its pharmacokinetic variability.

Rituximab, administered as an intravenous infusion at a dose of 375 mg/m^2 at weekly intervals for 4 doses to 203 patients with NHL naive to rituximab, yielded a mean C_{max} following the fourth infusion of 486 µg/mL (range, 77.5 to 996.6 µg/mL). Rituximab was detectable in the serum of patients 3 – 6 months after completion of last 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.

Chronic lymphocytic leukaemia

Rituximab was administered as an IV infusion at a first-cycle dose of 375 mg/m^2 increased to 500 mg/m^2 each cycle for 5 doses in combination with fludarabine and cyclophosphamide in CLL patients. The mean C_{max} (N=15) was 408 µg/ml (range, 97 – 764 µg/ml) after the fifth 500 mg/ m2 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 1000 mg, two weeks apart, the mean terminal half-life was 20.8 days (range, 8.58 to 35.9 days), mean systemic clearance was 0.23 L/day (range, 0.091 to 0.67 L/day), and mean steady-state distribution volume was 4.6 L (range, 1.7 to 7.51 L). The gender-related pharmacokinetic differences are not considered to be clinically relevant and dose adjustment is not required. Following the intravenous administration of 500 and 1000 mg doses of rituximab on two occasions, two weeks apart, mean Cmax values were 183 µg/mL (range, 81.8 to 279 µg/mL) and 370 µg/mL (212 to 637 µg/mL), and mean half-lives were 17.9 days (range, 12.3 to 31.3 days) and
19.7 days (range, 12.3 to 34.6 days), respectively. No pharmacokinetic data are available in patients with hepatic or renal impairment. No pharmacokinetic data are available for patients receiving multiple courses of therapy. The

pharmacokinetic (PK) parameters in the anti-TNF inadequate responder population, following the same dosage regimen (2 x 1000 mg, i.v., 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.

5.3 Preclinical safety data

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

Developmental toxicity studies have been performed in cynomolgus monkeys at dosages up to 100 mg/kg (treatment on gestation days 20-50) and have revealed no evidence of toxicity to the foetus due

to rituximab. However, dose-dependent pharmacologic depletion of B cells in the lymphoid organs of the foetuses were observed, which persisted post natally and was accompanied by a decrease in IgG level in the new born animals affected. B cell counts returned to normal in these animals within 6 months of birth and did not compromise the reaction to immunization.

No long-term animal studies have been performed to establish the carcinogenic potential of rituximab, or to determine its effects on fertility in males or females. Standard tests to investigate mutagenicity have not been carried out, since such tests are not relevant for this molecule. However, due to its character it is unlikely that rituximab has any mutagenic potential.

6.0 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The excipients used in the formulation of the Intas' rituximab 100 mg (10mg/mL) drug product are as per Indian, European, British and / or US Pharmacopoeia.
The details of specification of excipients of Intas' rituximab drug product are listed in below Table 3.

Table 3. List of Excipients

Sr. No.	Ingredients
1	Sodium citrate dihydrate
2	Polysorbate 80
3	Sodium chloride
4	Sodium hydroxide
5	Hydrochloric acid
6	Water for injection

6.2 Incompatibilities

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

6.3 Shelf life

18 months from the date of manufacture if stored at recommended storage condition.

The prepared infusion solution of rituximab is physically and chemically stable for 24 hours at 2 °C to 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 to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Intas' rituximab concentrate for solution for infusion should be stored in a refrigerator at 2 °C to 8 °C at all times. Do not freeze. Do not use if it has been frozen.
Protect from sunlight.

6.5 Nature and contents of container

Clear USP Type I borosilicate glass vials of 10 mL and 50 mL with Flurotec coated chlorobutyl rubber stopper containing 100 mg and 500 mg of rituximab respectively.

6.6 Special precautions for disposal

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

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 1-4 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.

7. Marketing Authorization Holder
INTAS PHARMACEUTICALS LTD

8. Marketing Authorization Number
H2019/CTD5925/1131ER

9. Date of first authorization/renewal of the authorization
2025 September 15

10. Date of revision of the text
2025 September 15