Schedule H Prescription Drug
Warning: *Preparation shall be supplied against the prescription of Cancer specialist / Rheumatologist*

Rituximab Injection

Ikgdar®

इक़्गदर®

1. DESCRIPTION

1.1 Therapeutic / Pharmacologic Class of Drug

Antineoplastic agent

ATC Code: L01XC02

1.2 Type of Dosage Form and Strengths

Dosage form: Intravenous (IV) formulation: Concentrate for solution for infusion.

Strength: 10mg/ml

1.3 Route of Administration

Intravenous formulation: Intravenous infusion.

1.4 Sterile / Radioactive Statement

Sterile product.

1.5 Qualitative and Quantitative Composition

Active ingredient: rituximab

Intravenous formulation

Ikgdar is a clear, colorless liquid supplied in sterile, preservative-free, non-pyrogenic single-dose vials.

Single-dose vials. Vials contain 100 mg/10 ml and 500 mg/50 ml.

Excipients: Sodium citrate, polysorbate 80, sodium chloride, sodium hydroxide, hydrochloric acid, water for injections.

2. CLINICAL PARTICULARS

2.1 Therapeutic Indication(s)

Ikgdar is indicated in adults for the following indications:

Non-Hodgkin's Lymphoma

Ikgdar IV is indicated for the treatment of:

- Patients with relapsed or chemoresistant Indolent B Cell Non-Hodgkin's Lymphoma
- treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy;
- maintenance therapy for the treatment of follicular lymphoma patients responding to induction therapy
- patients with CD20-positive diffuse large B-Cell Non-Hodgkin's Lymphoma in combination with CHOP chemotherapy.

Chronic Lymphocytic Leukaemia:

Ikgdar in combination with chemotherapy is indicated for the treatment of patients with previously untreated and relapsed/ refractory chronic lymphocytic leukaemia (CLL). Only limited data are available on efficacy and safety for patients previously treated with monoclonal antibodies including Ikgdar on patients refractory to previous Ikgdar plus chemotherapy.

Rheumatoid Arthritis

Ikgdar is indicated in adult patients for treatment of active rheumatoid arthritis in patients with an inadequate response or intolerance to one or more Tumour necrosis factor (TNF) inhibitor therapies. Ikgdar has been shown to reduce the rate of progression of joint damage as measured by X-ray, to improve physical function when given in combination with methotrexate.

Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA)

Ikgdar in combination with glucocorticoids is indicated for the treatment of adult patients with Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA).

2.2 Dosage and Administration

General

Intravenous formulation

Substitution by any other biological medicinal product requires the consent of the prescribing physician.

It is important to check the product labels to ensure that the appropriate formulation (IV) and strength is being given to the patient, as prescribed

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

The safety and efficacy of alternating or switching between Ikgdar and products that are biosimilar but not deemed interchangeable has not been established. Therefore, the benefit-risk of alternating or switching needs to be carefully considered.

Premedication and Prophylactic Medications:

Premedication consisting of an analgesic/anti-pyretic (*e.g., paracetamol/acectaminophen)* and an anti-histaminic drug, (e.g. *diphenhydramine)* should always be given before each administration of Ikgdar**.**

Premedication with glucocorticoids should be administered in order to reduce the frequency and severity of infusion-related reactions. Patients with RA, PV or adult should receive 100 mg IV methylprednisolone to be completed 30 minutes prior to each Ikgdar IV infusion (see *section 2.4 Warnings and Precautions*) .

In adult patients with NHL or CLL premedication with glucocorticoids should also be considered, particularly if Ikgdar is not given in combination with steroid containing chemotherapy (*see section 2.4 Warnings and Precautions*).

Pneumocystis jirovecii pneumonia (PJP) prophylaxis is recommended for adult patients with Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA) and adult patients with PV during and following Ikgdar IV treatment, as appropriate according to local clinical practice guidelines.

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 $x10^9$/L it is recommended to administer prednisone/ prednisolone 100 mg intravenously shortly before administration with Ikgdar to decrease the rate and severity of acute infusion reactions and/or cytokine release syndrome

Dosage adjustments during treatment:

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

Intravenous Formulation
Ikgdar IV formulation is not intended for subcutaneous administration *(see section 4.2 Special Instructions for Use, Handling and Disposal).*

Do not administer the prepared infusion solutions as an intravenous push or bolus (*see section 4.2 Special Instructions for Use, Handling and Disposal*).

Intravenous Formulation Infusion Rate

First intravenous infusion:

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

Subsequent intravenous infusions:

Subsequent infusions of Ikgdar can be started at a rate of 100 mg/hour, and increased by 100 mg/hour increments at 30 minutes intervals, to a maximum of 400 mg/hour.

Standard dosage

Intravenous Formulation

<u>Adult Indolent or follicular non-Hodgkin's lymphoma</u>

Initial treatment:

- *Intravenous monotherapy*

The recommended dosage of Ikgdar used as monotherapy for adult patients is 375 mg/m^2 body surface area (BSA), administered as an intravenous infusion (see *"Intravenous Formulation Infusion Rate" sub-section, above*) once weekly for 4 weeks.

- Intravenous combination therapy

The recommended dosage of Ikgdar in combination with any chemotherapy is 375 mg/m^2 BSA per cycle for a total of:

- 8 cycles R-IV with CVP (21 days/cycle)

- 8 cycles R-IV with MCP (28 days/cycle)
- 8 cycles R-IV with CHOP (21 days/cycle); 6 cycles if a complete remission is achieved after 4 cycles
- 6 cycles R-IV with CHVP-Interferon (21 days/cycle)

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

Re-treatment following relapse

Patients who have responded to Ikgdar initially may receive Ikgdar at a dose of 375 mg/m^2 BSA, administered as an IV infusion once weekly for 4 weeks (*see section 3.1.2 Clinical/Efficacy Studies, Re-treatment, weekly for 4 doses*).

Maintenance treatment:

Previously untreated patients after response to induction treatment may receive maintenance therapy with Ikgdar given at 375 mg/m^2 BSA once every 2 months until disease progression or for a maximum period of two years (12 infusions in total).

Relapsed/refractory patients after response to induction treatment may receive maintenance therapy with Ikgdar given at 375 mg/m^2 BSA once every 3 months until disease progression or for a maximum period of two years (8 infusions in total).

Adult Diffuse large B-cell non-Hodgkin's lymphoma

In patients with diffuse large B cell non-Hodgkin's lymphoma Ikgdar should be used in combination with CHOP *(cyclophosphamide, doxorubicin, prednisone and vincristine)* chemotherapy. The recommended dosage of Ikgdar is 375 mg/m^2 BSA, administered on day 1 of each chemotherapy cycle for 8 cycles after i.v. administration of the glucocorticoid component of CHOP. (see "*Intravenous Formulation Infusion Rate" sub-section, above*).

Chronic Lymphocytic Leukaemia:

Intravenous Formulation

The recommended dosage of Ikgdar IV in combination with chemotherapy for previously untreated and relapsed/ refractory CLL patients is 375 mg/m^2 BSA administered on day 1 of the first treatment cycle followed by 500mg/m^2 BSA administered on day 1 of each subsequent cycle for 6 cycles in total *(see Section 3.1.2 Clinical/Efficacy Studies)*. The chemotherapy should be given after Ikgdar IV infusion. (see "Intravenous Formulation Infusion Rate" sub-section, above)

Rheumatoid arthritis (RA):

Intravenous Formulation Only

A course of Ikgdar IV consists of two 1000 mg IV infusions. The recommended dosage of Ikgdar is 1000 mg by IV infusion followed two weeks later by the second 1000 mg IV infusion (*see "Intravenous Formulation Infusion Rate" sub-section, above*).

The need for further courses should be evaluated 24 weeks following the previous course with retreatment given based on residual disease or disease activity returning to a level above a DAS28-ESR of 2.6 (treatment to remission) (*see section 3.1.2 Clinical/Efficacy Studies, Rheumatoid Arthritis*), Patients may receive further courses no sooner than 16 weeks following the previous course.

Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA)

Wegener's Granulomatosis is also known as Granulomatosis with Polyangiitis (GPA)

Intravenous Formulation Only

Induction of Remission:

The recommended dosage of Ikgdar IV for treatment of adult patients with GPA and MPA is 375 mg/m^2 BSA, administered as an IV infusion (see "Intravenous Formulation Infusion Rate" sub-section, above) once weekly for 4 weeks.

Methylprednisolone given IV for 1 to 3 days at a dose of 1000mg per day is recommended in combination with Ikgdar IV to treat severe vasculitis symptoms followed by oral prednisone 1 mg/kg/day (not to exceed 80mg/day and tapered as rapidly as possible per clinical need) during and after the 4 week induction course of Ikgdar IV treatment

Maintenance Treatment:

Following induction of remission with Ikgdar IV, maintenance treatment should be initiated no sooner than 16 weeks after the last Ikgdar IV infusion.

Following induction of remission with other standard of care immunosuppressants, Ikgdar IV maintenance treatment should be initiated during the 4-week period that follows disease remission.

Administer Ikgdar IV as two 500 mg IV infusions separated by two weeks, followed by a 500 mg IV infusion at month 6, 12 and 18 and then every 6 months thereafter based on clinical evaluation

2.2.1 Special Dosage Instructions

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

2.3 Contraindications

Ikgdar is contraindicated in patients with known hypersensitivity to rituximab, to any of its excipients or to murine proteins.

2.4 Warnings and Precautions

2.4.1 General

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

Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukaemia Patients

Infusion/administration-related reactions:

Ikgdar is associated with infusion/administration-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.

- *Infusion-related reactions for Ikgdar IV:*

Severe infusion-related reactions (IRRs) with fatal outcome have been reported during post-marketing use. Severe IRRs usually manifested within 30 minutes to 2 hours after starting the first Ikgdar infusion, were characterized by *pulmonary events* and included, in some cases, *rapid tumor lysis* and *features of tumor lysis syndrome* in addition to fever, chills, rigors, hypotension, urticaria, angioedema and other symptoms *(see section 2.6 Undesirable Effects*). Patients with a high tumor burden or with a high number (>25 x 10^9/L) of circulating malignant cells such as patients with CLL and mantle cell lymphoma may be at higher risk of developing severe IRRs. Infusion reaction symptoms are usually reversible with interruption of the infusion. Treatment of infusion-related symptoms with diphenhydramine and paracetamol/acetaminophen is recommended. Additional treatment with bronchodilators or IV saline may be indicated. In most cases, the infusion can be resumed at a 50% reduction in rate (e.g. from 100 mg/hour to 50 mg/hour) when symptoms have completely resolved. Most patients who have experienced non-life threatening IRRs have been able to complete the full course of Ikgdar therapy. Further treatment of patients after complete resolution of signs and symptoms has rarely resulted in repeated severe IRRs.

Patients with a high number (>25 x 10^9/L) of circulating malignant cells or high tumor burden such as patients with CLL and mantle cell lymphoma, who may be at higher risk of especially severe IRRs, 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.

- *Hypersensitivity reactions / Anaphylaxis:*

Anaphylactic and other hypersensitivity reactions have been reported following the intravenous administration of proteins to patients. Epinephrine, antihistamines and glucocorticoids should be available for immediate use in the event of a hypersensitivity reaction to Ikgdar IV.

Pulmonary events:

Pulmonary events have included hypoxia, lung infiltration, and acute respiratory failure. Some of these events have been preceded by severe bronchospasm and dyspnea. In some cases, symptoms worsened over time, while in others initial improvement was followed by clinical deterioration. Therefore, patients experiencing pulmonary events or other severe infusion-related symptoms should be closely monitored until complete resolution of their symptoms occurs. Patients with a history of pulmonary insufficiency or those with pulmonary tumour infiltration may be at greater risk of poor outcome and should be treated with increased caution. Acute respiratory failure may be accompanied by events such as pulmonary interstitial infiltration or edema, visible on a chest x-ray. The syndrome usually manifests itself within one or two hours of initiating the first infusion. Patients who experience severe pulmonary events should have their Ikgdar administration interrupted immediately *(see section 2.2 Dosage and Administration)* and should receive aggressive symptomatic treatment.

Rapid tumor lysis

Ikgdar mediates the rapid lysis of benign and malignant CD20-positive cells. Signs and symptoms *(e.g. hyperuricemia, hyperkalemia, hypocalcemia, hyperphosphataemia, acute renal failure, elevated LDH)* consistent with tumour lysis syndrome (TLS) have been reported to occur after the first Ikgdar IV infusion in patients with high numbers of circulating malignant lymphocytes. Prophylaxis for TLS should be considered for patients at risk of developing rapid tumour lysis *(e.g. patients with a high tumor burden or with a high number (>25 x 10^9/L) of circulating malignant cells such as patients with CLL and mantle cell lymphoma)*. These patients should be followed closely and appropriate laboratory monitoring performed. Appropriate medical therapy should be provided for patients who develop signs and symptoms consistent with rapid tumour lysis. Following treatment and complete resolution of signs and symptoms, subsequent Ikgdar therapy has been administered in conjunction with prophylactic therapy for TLS in a limited number of cases.

Cardiovascular:
Since hypotension may occur during Ikgdar administration consideration should be given to withholding antihypertensive medications 12 hours prior to and throughout Ikgdar IV administration. Angina pectoris, cardiac arrhythmia, such as atrial flutter and fibrillation, heart failure or myocardial infarction have occurred in patients treated with Ikgdar IV. Therefore, patients with a history of cardiac disease should be monitored closely.

Monitoring of blood counts:

Although Ikgdar is not myelosuppressive in monotherapy, caution should be exercised when considering treatment of patients with neutrophil counts of $<1.5 \times 10^9$/L and/or platelet counts of $<75 \times 10^9$/L, as clinical experience with such patients is limited. Ikgdar has been used in patients who underwent autologous bone marrow transplantation and in other risk groups with a presumable reduced bone marrow function without inducing myelotoxicity.

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

Infections:

Ikgdar treatment should not be initiated in patients with severe active infections.

Hepatitis B Infections:

Cases of hepatitis B reactivation, including reports of fulminant hepatitis, some of which were fatal, have been reported in subjects receiving Ikgdar IV, although the majority of these subjects were also exposed to cytotoxic chemotherapy. The reports are confounded by both the underlying disease state and the cytotoxic chemotherapy.

Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with Ikgdar. 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 Ikgdar. Patients with positive hepatitis B serology should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation.

Progressive Multifocal Leukoencephalopathy:

Cases of Progressive Multifocal Leukoencephalopathy (PML) have been reported during use of Ikgdar IV in NHL and CLL (see section 2.6.2. *Undesirable Effects, Post Marketing*). The majority of patients had received Ikgdar IV in combination with chemotherapy or as part of a hematopoietic stem cell transplant. Physicians treating patients with NHL or CLL should consider PML in the differential diagnosis of patients reporting neurological symptoms and consultation with a Neurologist should be considered as clinically indicated.

Skin reactions:
Severe skin reactions such as toxic epidermal necrolysis and Stevens-Johnson syndrome, some with fatal outcome, have been reported *(see section 2.6 Undesirable Effects, Post Marketing).* In case of such an event with a suspected relationship to Ikgdar, treatment should be permanently discontinued.

Immunization:
The safety of immunization with live viral vaccines, following Ikgdar IV therapy has not been studied and vaccination with live virus vaccines is not recommended.

Patients treated with Ikgdar may receive non-live vaccinations. However, with non-live vaccines response rates may be reduced. In a non-randomized study, patients with relapsed low-grade NHL who received Ikgdar IV monotherapy when compared to healthy untreated controls had a lower rate of response to vaccination with tetanus recall antigen (16% Vs 81%) and Keyhole Limpet Haemocyanin (KLH) neoantigen (4% Vs 76% when assessed for >2-fold increase in antibody titer).

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 Ikgdar IV.

Rheumatoid Arthritis (RA), Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA) Patients

The efficacy and safety of Ikgdar IV for the treatment of autoimmune diseases other than rheumatoid arthritis, granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis have not been established.

Infusion related reactions:

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

For RA patients, most infusion-related events reported in clinical trials were mild to moderate in severity. Severe IRRs with fatal outcome have been reported in the post-marketing setting (*see section 2.6 Undesirable Effects, Post Marketing*). Closely monitor patients with pre-existing cardiac conditions and those who experienced prior

cardiopulmonary adverse reactions. The most common symptoms were headache, pruritus, throat irritation, flushing, rash, urticaria, hypertension, and pyrexia. In general, the proportion of patients experiencing any infusion reaction was higher following the first infusion of any treatment course than following the second infusion. Subsequent Ikgdar IV infusions were better tolerated by patients than the initial infusion. Less than 1% of patients experienced serious IRRs, with most of these reported during the first infusion of the first course *(see section 2.6 Undesirable Effects)*. The reactions reported were usually reversible with a reduction in rate, or interruption, of Ikgdar infusion and administration of an anti-pyretic, an antihistamine, and, occasionally, oxygen, intravenous saline, bronchodilators or glucocorticoids as required. Depending on the severity of the IRR and the required interventions, temporarily or permanently discontinue Ikgdar IV. In most cases, the infusion can be resumed at a 50% reduction in rate *(e.g. from 100 mg/hour to 50 mg/hour)* when symptoms have completely resolved.

Infusion-related reactions in GPA/MPA patients were consistent with those seen in RA patients in clinical trials and in the post-marketing setting (see section 2.6 Undesirable Effects).

Hypersensitivity reactions / Anaphylaxis:

Anaphylactic and other hypersensitivity reactions have been reported following the intravenous administration of proteins to patients. Medicinal products for the treatment of hypersensitivity reactions, *(e.g., epinephrine, antihistamines and glucocorticoids),* should be available for immediate use in the event of an allergic reaction during administration of Ikgdar IV.

Cardiovascular:

Since hypotension may occur during Ikgdar IV infusion, consideration should be given to withholding anti-hypertensive medications 12 hours prior to the Ikgdar infusion. Angina pectoris, cardiac arrhythmias such as atrial flutter and fibrillation, heart failure or myocardial infarction have occurred in patients treated with Ikgdar IV. Therefore, patients with a history of cardiac disease should be monitored closely (*see Infusion-related reactions sub-section, above)*

Infections:

Based on the mechanism of action of Ikgdar and the knowledge that B-cells play an important role in maintaining normal immune response, patients may have an increased risk of infection following Ikgdar IV therapy (*see section 3.1.1 Mechanism of Action*). Ikgdar should not be administered to patients with an active infection or severely immunocompromised patients *(e.g. where levels of CD4 or CD8 are very low).* Physicians should exercise caution when considering the use of Ikgdar in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection, *(see section 2.6 Undesirable Effects*

Patients who develop infection following Ikgdar IV therapy should be promptly evaluated and treated appropriately.

Hepatitis B infections:
Cases of hepatitis B reactivation including those with a fatal outcome have been reported in RA, GPA and MPA patients receiving Ikgdar IV.

Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with Ikgdar IV. 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 Ikgdar IV. Patients with positive hepatitis B serology should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation.

Skin reactions:
Severe skin reactions such as toxic epidermal necrolysis and Stevens-Johnson syndrome, some with fatal outcome, have been reported *(see section 2.6 Undesirable Effects, Post Marketing)*. In case of such an event with a suspected relationship to Ikgdar IV, treatment should be permanently discontinued.

Progressive Multifocal Leukoencephalopathy
Cases of fatal progressive multifocal leukoencephalopathy (PML) have been reported following use of Ikgdar IV for the treatment of autoimmune diseases including RA. Several, but not all of the reported cases had potential risk factors for PML, including the underlying disease, long-term immunosuppressive therapy or chemotherapy. PML has also been reported in patients with autoimmune disease not treated with Ikgdar IV. Physicians treating patients with autoimmune diseases should consider PML in the differential diagnosis of patients reporting neurological symptoms and consultation with a neurologist should be considered as clinically indicated.

Immunization:
The safety of immunization with live viral vaccines following Ikgdar IV therapy has not been studied. Therefore, vaccination with live virus vaccines is not recommended whilst receiving Ikgdar or whilst peripherally B cell depleted. Patients treated with Ikgdar may receive non-live vaccinations. However, response rates to non-live vaccines may be reduced.

For patients treated with Ikgdar IV, physicians should review the patient's vaccination status and patients should, if possible, be brought up-to-date with all immunizations in agreement with current immunization guidelines prior to initiating Ikgdar IV therapy. Vaccinations should be completed at least 4 weeks prior to first administration of Ikgdar IV.

In a randomized study, patients with RA treated with Ikgdar and methotrexate had comparable response rates to tetanus recall antigen (39% vs 42%), reduced rates to

pneumococcal polysaccharide vaccine (43% vs 82% to at least 2 pneumococcal antibody serotypes), and KLH neoantigen (34% vs 80%), when given at least 6 months after Ikgdar IV as compared to patients only receiving methotrexate. Should non-live vaccinations be required whilst receiving Ikgdar therapy, these should be completed at least 4 weeks prior to commencing the next course of Ikgdar IV.

In the overall experience of Ikgdar IV repeat treatment in RA patients over one year, 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.

Methotrexate naïve RA populations:
The use of Ikgdar IV is not recommended in methotrexate-naïve patients since a favourable benefit risk relationship has not been established.

2.4.2 Drug Abuse and Dependence

No data to report.

2.4.3 Ability to Drive and Use Machines

Ikgdar has no or negligible effect on the ability to drive and use machines.

2.5 Use in Special Populations

2.5.1 Females and Males of Reproductive Potential

Intravenous Formulation

- ***Fertility***
  No preclinical fertility studies have been conducted.

- ***Animal data***
  Developmental toxicity studies performed in cynomolgus monkeys revealed no evidence of embryotoxicity in utero. Newborn offspring of maternal animals exposed to Ikgdar were noted to have depleted B-cell populations during the post natal phase.

Contraception
Women of childbearing age must employ effective contraceptive methods during and for 12 months after treatment with Ikgdar.

2.5.2 Pregnancy

Intravenous Formulation

IgG immunoglobulins are known to cross the placental barrier.

B cell levels in human neonates following maternal exposure to Ikgdar 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 Ikgdar should not be administered to pregnant women unless the possible benefit outweighs the potential risk.

2.5.3 Lactation

Maternal IgG enters breast milk, and rituximab has been reported to excreted at low concentrations in human breast milk. Given that the clinical significance of this finding for infants is not known, Ikgdar should not be administered to nursing mothers.

2.5.4 Geriatric Use

Hypogammaglobulinaemia has been observed in pediatric patients treated with Ikgdar IV, in some cases severe and requiring long-term immunoglobulin substitution therapy. The consequences of long term B-cell depletion in pediatric patients are unknown.

The safety and efficacy of Ikgdar in geriatric patients has not been established.

2.5.5 Renal Impairment

The safety and efficacy of renal impairment in Ikgdar patients has not been established.

2.5.6 Hepatic Impairment

The safety and efficacy of hepatic impairment in Ikgdar patients has not been established.

2.6 Undesirable Effects

2.6.1 Clinical Trials

Experience from Clinical Trials in Haemato-Oncology in Adults

Intravenous Formulation

The frequencies of adverse drug reactions (ADRs) reported with Ikgdar IV alone or in combination with chemotherapy are summarised in the tables below and are based on data from clinical trials. These ADRs had either occurred in single arm studies or had occurred with at least a 2% difference compared to the control arm in at least one of the major randomized clinical trials. ADRs are added to the appropriate category in the tables below according to the highest incidence seen in any of the major clinical trials. Within each frequency grouping ADRs are listed in descending order of severity. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1,000 to < 1/100).

Ikgdar monotherapy / maintenance therapy

The ADRs in the table 1, are based on data from single-arm studies including 356 patients with low-grade or follicular lymphoma, treated with Ikgdar IV weekly as single agent for the treatment or re-treatment of Non-Hodgkin's Lymphoma *(see section 3.1.2 Clinical/Efficacy Studies*). The table also contains ADRs based on data from 671 patients with follicular lymphoma who received Ikgdar as maintenance therapy for up to 2 years following response to initial induction with CHOP, R-CHOP, R-CVP or R-FCM *(see section 3.1.2 Clinical/Efficacy Studies*). The ADRs were reported up to 12 months after treatment with monotherapy and up to 1 month after treatment with Ikgdar maintenance.

Table 1 Summary of ADRs reported in patients with low-grade or follicular lymphoma receiving Ikgdar IV monotherapy (N = 356) or Ikgdar IV maintenance treatment (N =671) in clinical trials.

System Organ Class	Very Common (≥ 10%)	Common (≥1% - < 10%)	Uncommon (≥0.1% - < 1%)
Infections and infestations	bacterial infections, viral infections ,	sepsis , [+]pneumonia, [+]febrile infection, [+]herpes zoster, [+]respiratory tract infection, fungal infections, infections of unknown aetiology	
Blood and the lymphatic system disorders	neutropenia , leucopenia	anaemia, thrombocytopenia	coagulation disorders, transient aplastic anaemia, haemolytic anaemia, lymphadenopathy
Immune system disorders	angioedema	hypersensitivity	
Metabolism and nutrition disorders		hyperglycaemia, weight decrease, peripheral edema, face edema, increased LDH, hypocalcemia	
Psychiatric disorders			depression, nervousness
Nervous system disorders		paresthesia, hypoesthesia, agitation, insomnia, vasodilatation, dizziness, anxiety	dysgeusia
Eye disorders		lacrimation disorder, conjunctivitis	
Ear and labyrinth disorders		tinnitus, ear pain	
Cardiac disorders		[+]myocardial infarction, arrhythmia , [+]atrial fibrillation, tachycardia, [+]cardiac disorder	[+]left ventricular failure, [+]supraventricular tachycardia, [+]ventricular tachycardia, [+]angina, [+]myocardial ischaemia,

			bradycardia,
Vascular disorders		hypertension , orthostatic hypotension, hypotension	
Respiratory, thoracic and mediastinal disorders		bronchospasm , respiratory disease, chest pain, dyspnoea , cough , rhinitis	asthma , bronchiolitis obliterans, lung disorder, hypoxia
Gastrointestinal disorders	nausea	vomiting , diarrhea, abdominal pain , dysphagia , stomatitis, constipation dyspepsia, anorexia, throat irritation	abdominal enlargement
Skin and subcutaneous tissue disorders	pruritis , rash	urticaria , +alopecia, sweating, night sweats	
Musculoskeletal, connective tissue and bone disorders		hypertonia, myalgia , arthralgia , back pain , neck pain, pain	
General disorders and administration site conditions	fever , chills , asthenia , headache	tumour pain, flushing, malaise, cold syndrome	infusion site pain
Investigations	decreased IgG levels		

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

Ikgdar IV in combination with chemotherapy in NHL and CLL

The ADRs listed in the table 2 are based on Ikgdar IV-arm data from controlled clinical trials that occurred in addition to those seen with monotherapy / maintenance therapy and/or at a higher frequency grouping: 202 patients with diffuse large B-cell lymphoma (DLBCL) treated with R-CHOP, and from 234 and 162 patients with follicular lymphoma treated with R-CHOP or R-CVP, respectively and from 397 previously untreated CLL patients and 274 relapsed/refractory CLL patients, treated with Ikgdar IV in combination with fludarabine and cyclophosphamide (R-FC) *(see section 3.1.2 Clinical/Efficacy Studies*).

Table 2 Summary of severe ADRs reported in patients receiving R-CHOP in DLBCL (N=202), R-CHOP in follicular lymphoma (N=234) and R-CVP in follicular lymphoma (N=162), R-FC in previously untreated

(N=397) or relapsed/refractory (N= 274) chronic lymphocytic leukaemia

System Organ Class	Very Common (≥ 10%)	Common (≥ 1% - <10%)
Infections and infestations	bronchitis	acute bronchitis, sinusitis, hepatitis B*,
Blood and the lymphatic system disorders	Neutropenia#, febrile Neutropenia, thrombocytopenia	pancytopenia, granulocytopenia
Skin and subcutaneous tissue disorders	Alopecia	skin disorder
General disorders and administration site conditions		fatigue, shivering,

*includes reactivation and primary infections; frequency based on R-FC regimen in relapsed/refractory CLL Frequency count was based on only severe reactions defined in clinical trials as ≥ grade 3 NCI common toxicity criteria. Only the highest frequency observed in any trial is reported

prolonged and/or delayed onset neutropenia after completion of an R-FC course in previously untreated or relapsed/refractory CLL

The following terms have been reported as adverse events, however, were reported at a similar (<2% difference between the groups) or lower incidence in the Ikgdar IV-arms compared to control arms: *Haematotoxicity, neutropenic infection, urinary tract infection, septic shock, superinfection lung, implant infection, septicaemia staphylococcal, lung infection, rhinorrheoa, pulmonary oedema, cardiac failure, sensory disturbance, venous thrombosis, mucosal inflammation nos, influenza-like illness, oedema lower limb, abnormal ejection fraction, pyrexia, general physical health deterioration, fall, multi-organ failure, venous thrombosis deep limb, positive blood culture, diabetes mellitus inadequate control.*

The safety profile for Ikgdar in combination with other chemotherapies (e.g. MCP, CHVP-IFN) is comparable to the safety profile as described for the combination of Ikgdar IV and CVP, CHOP or FC in equivalent populations.

Experience from Pediatric diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL)/Burkitt leukemia (mature B-cell acute leukaemia) (BAL) or Burkitt-like lymphoma (BLL)

A multicenter, open-label randomized study of Lymphome Malin B (LMB) chemotherapy with or without Rituximab IV was conducted in pediatric patients (aged ≥ 6 months to < 18 years old) with previously untreated advanced stage CD20 positive DLBCL/BL/BAL/BLL. A total of 309 pediatric patients received Rituximab IV and were included in the safety analysis population. Pediatric patients randomized to the LMB chemotherapy arm with Rituximab, or enrolled in the single arm part of the study, were administered Rituximab at a dose of 375mg/m^2 BSA and received a total of six IV

infusions of Rituximab (two during each of the two induction courses and one during each of the two consolidation courses of the LMB scheme).

The safety profile of Rituximab IV in pediatric patients (aged ≥ 6 months to < 18 years old) with previously untreated DLBCL/BL/BAL/BLL was generally consistent in type, nature and severity with the known safety profile in adult NHL and CLL patients. Addition of Rituximab IV to chemotherapy did result in an increased risk of some adverse events such as infections (including sepsis) compared to chemotherapy only. There were no pediatric specific ADRs identified and the current list of ADRs for adult oncology patients is applicable to the pediatric B-NHL population.

Subcutaneous Formulation (not approved and not available in India)

Local cutaneous reactions, including injection site reactions, were very common (≥ 1/10) in patients receiving Rituximab SC. In the phase 3 SABRINA (BO22334) study, local cutaneous reactions were reported in up to 23% of patients receiving Rituximab SC. The most common local cutaneous reactions in the Rituximab SC arm were: *injection site erythema* (13%), *injection site pain* (8%), *and injection site oedema* (4%). Similar events were observed in the SAWYER (BO25341) study and were reported in up to 42% of patients in the Rituximab SC arm. The most common local cutaneous reactions were: *injection site erythema* (26%), *injection site pain* (16%), and *injection site swelling* (5%).

Events seen following subcutaneous administration were mild or moderate, apart from one patient in the SABRINA study who reported a local cutaneous reaction of Grade 3 intensity (*injection site rash*) and two patients in the SAWYER study who experienced Grade 3 local cutaneous reactions (*injection site erythema*, *injection site pain*, and *injection site swelling*). Local cutaneous reactions of any Grade in the Rituximab SC arm were most common during the first subcutaneous cycle (Cycle 2), followed by the second, and the incidence decreased with subsequent injections.

The safety profile of Rituximab SC was otherwise comparable to that of the IV formulation

No cases of anaphylaxis or severe hypersensitivity reactions, cytokine release syndrome or tumour lysis syndrome were observed following subcutaneous administration during the Rituximab SC development program.

Further information on selected, serious adverse drug reactions

Intravenous Formulation

Administration-related reactions

Monotherapy - 4 weeks treatment

Signs and symptoms suggestive of an infusion-related reaction (IRR) were reported in more than 50% of patients in clinical trials, and were predominantly seen during the first

infusion. Hypotension, fever, chills, rigors, urticaria, bronchospasm, sensation of tongue or throat swelling (angioedema), nausea, fatigue, headache, pruritus, dyspnea, rhinitis, vomiting, flushing, and pain at disease sites have occurred in association with Ikgdar IV infusion as part of an infusion-related symptom complex. Some features of tumor lysis syndrome have also been observed.

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

Severe IRRs occurred in up to 12% of all patients at the time of the first treatment cycle with Ikgdar IV in combination with chemotherapy. The incidence of severe infusion-related reactions decreased substantially with subsequent infusions and in <1% by the eighth cycle. Additional reactions reported were: dyspepsia, rash, hypertension, tachycardia, and features of tumour lysis syndrome. Isolated cases of myocardial infarction, atrial fibrillation, pulmonary oedema and acute reversible thrombocytopenia were also reported.

Subcutaneous Formulation (not approved and not available in India)

The risk of acute administration-related reactions associated with the subcutaneous formulation of Rituximab was assessed in three clinical studies.

In the SparkThera (BP22333) study no severe administration-related reactions were reported.

In the SABRINA (BO22334) study severe administration-related reactions (Grade ≥3) were reported in two patients (1%) following Rituximab SC administration. These events were Grade 3 *injection site rash* and *dry mouth*.

In the SAWYER (BO25341) study severe administration-related reactions (Grade ≥3) were reported in four patients (5%) following Rituximab SC administration.

These events were Grade 4 *thrombocytopenia* and Grade 3 *anxiety, injection-site erythema* and *urticarial.*

Intravenous Formulation

Combination Therapy at 90-Minute Infusion Rate (R-CVP in f-NHL; R-CHOP in DLBCL)

In a study to characterize the safety profile of 90-minute Ikgdar IV infusions in patients who well tolerated their first standard Ikgdar IV infusion (Study U4391g), the incidence of Grade 3 and4 IRRs on the day of and/or the day after the 90-minute Ikgdar IV infusion at Cycle 2 in the 363 evaluable patients was 1.1% (95% CI [0.3%, 2.8%]). The incidence of Grade 3 and 4 IRRs at any cycle (Cycles 2 to 8) at the 90-minute infusion rate was 2.8% (95% CI [1.3%, 5.0%]). No acute fatal IRRs were observed (*see section 3.1.2 Clinical/Efficacy Studies*)

Infections

Monotherapy 4 weeks treatment

Ikgdar induced B-cell depletion in 70% to 80% of patients but was associated with decreased serum immunoglobulins in only a minority of patients. Bacterial, viral, fungal and unknown etiology infections, irrespective of causal assessment, occurred in 30.3% of 356 patients. Severe infectious events (grade 3 or 4), including sepsis occurred in 3.9% of patients.

Maintenance Treatment (NHL) up to 2 years

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

Data from clinical trials included cases of fatal PML in NHL patients that occurred after disease progression and retreatment (*see section 2.4 Warnings and Precautions*).

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

No increase in the frequency of infections or infestations was observed. The most common infections were upper respiratory tract infections which were reported for 12.3% patients on R-CVP and 16.4% patients receiving CVP;. Serious infections were reported in 4.3% of the patients receiving R-CVP and 4.4% of the patients receiving CVP. No life-threatening infections were reported during this study.

In the R-CHOP study the overall incidence of grade 2 to 4 infections was 45.5% in the R-CHOP group and 42.3% in the CHOP group. Grade 2 to 4 fungal infections were more frequent in the R-CHOP group (4.5% vs 2.6% in the CHOP group); this difference was due to a higher incidence of localized Candida infections during the treatment period. The incidence of grade 2 to 4 herpes zoster, , was higher in the R-CHOP group (4.5%) than in the CHOP group (1.5%). The proportion of patients with grade 2 to 4 infections and/or febrile neutropenia was 55.4% in the R-CHOP group and 51.5% in the CHOP group..

In patients with CLL, the incidence of grade 3 or 4 hepatitis B infection (reactivation and primary infection) was 2% R-FC vs 0% in the FC group.

Hematologic events

Monotherapy 4 weeks

Severe (grade 3 and 4) neutropenia was reported in 4.2% of patients, severe anemia was reported in 1.1% of patients and severe thrombocytopenia was reported in 1.7% of patients.

Maintenance Treatment (NHL) up to 2 years

There was a higher incidence of grade 3 and 4 leucopenia (observation 2% vs. Ikgdar IV 5%) and neutropenia (observation 4% vs. Ikgdar IV 10%) in the Ikgdar arm compared to the observation arm. The incidence of grade 3 and 4 thrombocytopenia (observation 1%, vs. Ikgdar IV <1%) was low. In approximately half of the patients with available data on B-cell recovery after end of Ikgdar IV induction treatment, it took 12 months or more for their B-cell levels to return to normal values.

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

During treatment course in studies with Ikgdar IV in combination with chemotherapy, Grade 3 and 4 leucopenia (R-CHOP 88% vs. CHOP 79%, R-FC 23% vs. FC 12%) and neutropenia (R-CVP 24% vs. CVP 14%; R-CHOP 97% vs. CHOP 88%, R-FC 30% vs. FC 19% in previously untreated CLL) were usually reported with higher frequencies when compared to chemotherapy alone. However, the higher incidence of neutropenia in patients treated with Ikgdar IV and chemotherapy was not associated with a higher incidence of infections and infestations compared to patients treated with chemotherapy alone. Studies in previously untreated and relapsed/refractory CLL have established that in some cases neutropenia was prolonged or with a late onset following treatment in the Ikgdar IV plus FC group

No relevant difference between the treatment arms was observed with respect to grade 3 and 4 anaemia or thrombocytopenia. In the CLL first-line study, grade 3 and 4 anaemia was reported by 4% of patients treated with R-FC compared to 7% of patients receiving FC, and grade 3and 4 thrombocytopenia was reported by 7% of patients in the R-FC group compared to 10% of patients in the FC group. In the relapsed/refractory CLL study, adverse events of grade 3and 4 anaemia were reported in 12% of patients treated with R-FC compared to 13% of patients receiving FC and grade 3 and 4 thrombocytopenia was reported by 11% of patients in the R-FC group compared to 9% of patients in the FC group.

<u>Cardiovascular events</u>

Monotherapy 4 week treatment

Cardiovascular events were reported in 18.8% of patients during the treatment period. The most frequently reported events were: hypotension and hypertension. Cases of grade 3 and 4 arrhythmia *(including ventricular and supraventricular tachycardia)* and angina pectoris during a Ikgdar IV infusion were reported.

Maintenance Treatment (NHL) up to 2 years

The incidence of grade 3 and 4 cardiac disorders was comparable between the two treatment groups. Cardiac events were reported as serious adverse event in <1% of patients on observation and in 3% of patients on Ikgdar IV: *atrial fibrillation (1%), myocardial infarction (1%), left ventricular failure (<1%), myocardial ischemia (<1%).*

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

In the R-CHOP study the incidence of grade 3 and 4 cardiac arrhythmias, predominantly supraventricular arrhythmias such as tachycardia and atrial flutter/fibrillation, was higher in the R-CHOP group (6.9%) as compared to the CHOP group (1.5%). All arrhythmias either occurred in the context of a Ikgdar IV infusion or were associated with predisposing conditions such as fever, infection, acute myocardial infarction or pre-existing respiratory and cardiovascular disease *(see section 2.4 Warnings and Precautions)*. No difference between the R-CHOP and CHOP group was observed in the incidence of other grade 3 and 4 cardiac events including heart failure, myocardial disease and manifestations of coronary artery disease.

In CLL, the overall incidence of grade 3 or 4 cardiac disorders was low both in the first-line study (4% R-FC vs. 3% FC) and in the relapsed/refractory study (4% R-FC, vs. 4% FC).

IgG levels

Maintenance Treatment (NHL) up to 2 years

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

Neurologic events

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

During the treatment period, 2% of patients in the R-CHOP group, all with cardiovascular risk factors, experienced thromboembolic cerebrovascular accidents during the first treatment cycle. There was no difference between the treatment group in the incidence of other thromboembolic events. In contrast, 1.5% of patients had cerebrovascular events in the CHOP group, all of which occurred during the follow-up period.

In CLL, the overall incidence of grade 3 and 4 nervous system disorders was low both in the first-line study (4% R-FC, vs. 4% FC) and in the relapsed/refractory study (3% R-FC, vs. 3% FC).

Subpopulations

Monotherapy 4 weeks treatment

Elderly patients (≥65 years):

The incidence of any ADR and of grade 3 and 4 ADRs was similar in elderly (≥65 years of age) and younger patients (88.3% versus 92.0% for any ADR and 16.0% versus 18.1% for grade 3 and 4 ADRs).

Combination Therapy

Elderly patients (≥65 years):

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

Bulky disease

Patients with bulky disease had a higher incidence of grade 3 and 4 ADRs than patients without bulky disease (25.6% versus 15.4%). The incidence of any ADR was similar in these two groups (92.3% in bulky disease versus 89.2% in non-bulky disease).

Re-treatment with Monotherapy:

The percentage of patients reporting any ADR and grade 3 and 4 ADRs upon re-treatment with further courses of Ikgdar IV was similar to the percentage of patients reporting any ADR and grade 3 and 4 ADRs upon initial exposure (95.0% versus 89.7% for any ADR and 13.3% versus 14.8% for grade 3 and 4 ADRs).

Experience from Rheumatoid Arthritis Clinical Trials

Intravenous Formulation

The safety profile of Ikgdar IV in the treatment of patients with moderate to severe RA is summarized in the sections below. In the all-exposure population more than 3000 patients received at least one treatment course and were followed for periods ranging from 6 months to over 5 years with an overall exposure equivalent to 7198 patient years; approximately 2300 patients received two or more courses of treatment during the follow up period.

The ADRs listed in Table 3 are based on data from placebo-controlled periods of four multicenter, RA clinical trials. The patient populations receiving Ikgdar IV differed between studies, ranging from early active RA patients who were methotrexate (MTX) naïve, through MTX inadequate responders (MTX-IR) to patients who had inadequate response to anti-tumour necrosis factor (TNF) therapies (TNF-IR) (*see section 3.1.2 Clinical/Efficacy Studies*).

Patients received 2 x 1000 mg or 2 x 500 mg of Ikgdar IV separated by an interval of two weeks; in addition to methotrexate (10 to 25 mg/week) (*see section 2.2 Dosage and Administration, Rheumatoid Arthritis*).

The ADRs listed in Table 3 are those which occurred at a rate of at least 2%, with at least 2% difference compared to the control arm and are presented regardless of dose. Frequencies in Table 3 and corresponding footnote 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 3 Summary of ADRs reported in patients with rheumatoid arthritis within Control Period of Clinical Trial †

System Organ Class	Very Common	Common
Infections and Infestations	Upper respiratory tract infection, Urinary tract infection	Bronchitis. Sinusitis, Gastroenteritis, Tinea pedis
Immune System Disorders/ General disorders and administration site conditions	Infusion related reactions	*Infusion related reactions (Hypertension, Nausea, Rash, Pyrexia, Pruritus, Urticaria, Throat irritation, Hot flush, Hypotension, Rhinitis, Rigors, Tachycardia, Fatigue, Oropharyngeal pain, Peripheral Oedema, Erythema)
Metabolism and Nutritional Disorders		Hypercholesterolemia
Nervous System disorders	Headache	Paraesthesia, Migraine, Dizziness, Sciatica,
Skin & Subcutaneous Tissue disorders		Alopecia
Psychiatric Disorders		Depression, Anxiety
Gastrointestinal Disorders		Dyspepsia, Diarrhoea, Gastro-oesophageal reflux, Mouth ulceration, upper abdominal pain
Musculo skeletal disorders		Arthralgia/ Musculoskeletal pain, Osteoarthritis, Bursitis
† This table includes all events with an incidence difference of ≥2 % for Ikgdar IV compared to placebo. * In addition, medically significant events reported uncommonly associated with IRRs include: generalized oedema, bronchospasm, wheezing, laryngeal oedema, angioneurotic oedema, generalized pruritus, anaphylaxis, anaphylactoid reaction.		

In the all-exposure population the safety profile was consistent with that seen in the controlled period of the clinical trials with no new ADRs identified

Multiple Courses:

Multiple courses of treatment are associated with a similar ADR profile to that observed following first exposure. The safety profile improved with subsequent courses due to a

decrease in IRRs, RA exacerbation and infections, all of which were more frequent in the first 6 months of treatment

Further information on selected adverse drug reactions:

Infusion-related reactions:

The most frequent ADRs following receipt of Ikgdar IV in RA clinical studies were IRRs. Among the 3095 patients treated with Ikgdar, 1077 (35%) experienced at least one IRR. The vast majority of IRRs were CTC Grade 1 or 2. In clinical studies less than 1% (14/3095 patients) of patients with RA who received an infusion of Ikgdar IV at any dose experienced a serious IRR. There were no CTC Grade 4 IRRs and no deaths due to IRRs in the clinical studies (*see section 2.6 Undesirable Effects, Post-Marketing*). The proportion of CTC Grade 3 events, and IRRs leading to withdrawal decreased by course and were rare from course 3 onwards.

Signs and/or symptoms suggesting an IRR (i.e., *nausea, pruritus, fever, urticaria/rash, chills, pyrexia, rigors, sneezing, angioneurotic oedema, throat irritation, cough and bronchospasm, with or without associated hypotension or hypertension*) were observed in 720/3095 (23%) patients following the first infusion of the first exposure to Ikgdar IV. Premedication with IV glucocorticoid significantly reduced the incidence and severity of these events (*see section 2.4 Warnings and Precautions*).

In a study designed to evaluate the safety of a 120-minute Ikgdar IV infusion in patients with RA, patients with moderate-to-severe active RA who did not experience a serious IRR during or within 24 hours of their first studied infusion were allowed to receive a 120-minute infusion of Ikgdar IV. Patients with a history of a serious infusion reaction to a biologic therapy for RA were excluded from entry. The incidence, types and severity of IRRs were consistent with that observed historically. No serious IRRs were observed (*see section 3.1.2 Clinical/Efficacy Studies*)

Infections:

The overall rate of infection was approximately 97 per 100 patient years in Ikgdar IV treated patients. The infections were predominately mild to moderate and consisted mostly of upper respiratory tract infections and urinary tract infections. The rate of serious infections was approximately 4 per 100 patient years, some of which were fatal. In addition to the ADRs in Table 3, medically serious events reported also include pneumonia at a frequency of 1.9%

Malignancies:
The incidence of malignancy following exposure to Ikgdar IV in RA clinical studies (0.8 per 100 patient years) lies within the range expected for an age and gender-matched population

Clinical Trial Experience in Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA)

Intravenous Formulation

Adult Induction of Remission (GPA/MPA Study 1):

In GPA/MPA Study 1, 99 adult GPA/MPA patients were treated for induction of remission of GPA and MPA with Ikgdar IV (375 mg/m^2, once weekly for 4 weeks) and glucocorticoids (*see section 3.1.2 Clinical/Efficacy Studies*)

The ADRS presented below in Table 4 were all adverse events which occurred at a an incidence of $\geq$ 10% in the Ikgdar IV-treated group. Frequencies in Table 4 are defined as very common (≥1/10).

Table 4: Incidence of Very Common (≥ 10%) ADRs for Ikgdar IV-treated Adult patients in GPA/MPA Study 1 up to Month 6*

Adverse reactions	Rituximab N=99	Cyclophosphamide N=98
Infections and infestations		
Infections [a]	61 (61.6%)	46 (46.9%)
Gastrointestinal disorders		
Nausea	18 (18.2%)	20 (20.4%)
Diarrhea	17 (17.2%)	12 (12.2%)
Nervous system disorders		
Headache	17 (17.2%)	19 (19.4%)
Musculoskeletal and connective tissue disorders		
Muscle spasms	17 (17.2%)	15 (15.3%)
Arthralgia	13 (13.1%)	9 (9.2%)
Blood and lymphatic system disorders		
Anemia	16 (16.2%)	20 (20.4%)
Leukopenia	10 (10.1%)	26 (26.5%)
General disorders and administration site conditions		
Peripheral edema	16 (16.2%)	6 (6.1%)
Fatigue	13 (13.1%)	21 (21.4%)
Psychiatric disorders		

Insomnia	14 (14.1%)	12 (12.2%)
Investigations Increased ALT	 13 (13.1%)	 15 (15.3%)
Respiratory, thoracic and mediastinal disorders Cough Epistaxis Dyspnea	 13 (13.1%) 11 (11.1%) 10 (10.1%)	 11 (11.2%) 6 (6.1%) 11 (11.2%)
Vascular disorders Hypertension	 12 (12.1%)	 5 (5.1%)
Injury, poisoning and procedural complications Infusion related reactions [b]	 12 (12.1%)	 11 (11.2%)
Skin and subcutaneous tissue disorders Rash	 10 (10.1%)	 17 (17.3%)
*The study design allowed for crossover or treatment by best medical judgment, and 13 patients in each treatment group received a second therapy during the 6 month study period. [a] Most common infections in the rituximab group of the induction of remission clinical trial included upper respiratory tract infections, urinary tract infections, and herpes zoster. [b] Most common terms reported in the rituximab group of the induction of remission clinical trial included cytokine release syndrome, flushing, throat irritation, and tremor		

Adult Maintenance Treatment (GPA/MPA Study 2):
In GPA/MPA Study 2, a total of 57 adult patients with severe active GPA and MPA were treated for the maintenance of remission (see section 3.1.2 Clinical/Efficacy Studies).

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

ADRs were all adverse events which occurred at an incidence of ≥ 10% in the Ikgdar IV-treated group. The very commonly (≥ 10%) reported events considered ADRs were: infusion-related reactions and infections.

Adult Long-term Follow-up (GPA/MPA Study 3):
In a long-term observational safety study, 97 adult GPA/MPA patients received treatment with Ikgdar (mean of 8 infusions [range 1-28]) for up to 4 years, according to their

physician's standard practice and discretion. The overall safety profile was consistent with the well-established safety profile of Ikgdar in RA and GPA/MPA and no new adverse drug reactions were reported.

Pediatric Population
An open-label, single arm study was conducted in 25 pediatric patients with active GPA/MPA. The overall study period consisted of a 6-month remission induction phase and a minimum 18-month follow-up phase, up to 4.5 yrs. During the follow-up phase, Ikgdar was given at the discretion of the investigator (17 out of 25 patients received additional Ikgdar treatment). Concomitant treatment with other immunosuppressive therapy was permitted (see *section 3.1.2 Clinical/Efficacy Studies*).

All identified ADRs were considered all adverse events that occurred at an incidence of ≥ 10%. These included: infections (17 patients [68%] in the remission induction phase; 23 patients [92%] in the overall study period), IRRs (15 patients [60%] in the remission induction phase; 17 patients [68%] in the overall study period), and nausea (4 patients [16%] in the remission induction phase; 5 patients [20%] in the overall study period).

During the overall study period, the safety profile of Ikgdar IV was consistent with that reported during the remission induction phase. The safety profile of Ikgdar IV in pediatric GPA/MPA patients was consistent in type, nature and severity with the known safety profile in adult patients with autoimmune diseases in the approved indications, including adult GPA/MPA.

Further information on selected adverse drug reactions:

Infusion-related reactions:

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

In GPA/MPA Study 2 (adult maintenance study), 7/57 (12%) patients in the Ikgdar IV arm reported infusion-related reactions. The incidence of IRR symptoms was highest during or after the first infusion (9%) and decreased with subsequent infusions (<4%). All IRR symptoms were mild to moderate and most were reported from the Respiratory, Thoracic and Mediastinal Disorders and Skin and Subcutaneous Tissue disorders SOCs.

In the pediatric GPA/MPA study, the reported IRRs were predominantly seen with the first infusion (8 patients [32%]), and then decreased over time with the number of Ikgdar IV infusions (20% with the second infusion, 12% with the third infusion and 8% with the fourth infusion). The most common IRR symptoms reported during the remission induction phase were: headache, rash, rhinorrhea and pyrexia (8%, for each symptom).

The observed symptoms of IRRs were similar to those known in adult GPA/MPA patients treated with Ikgdar IV. The majority of IRRs were Grade 1 and Grade 2, there were two non-serious Grade 3 IRRs, and no Grade 4-5 IRRs reported. One serious Grade 2 IRR (generalized oedema which resolved with treatment) was reported in one patient (see section *2.4 Warning and Precautions*).

Infections:
In GPA/MPA Study 1, the overall rate of infection was approximately 210 per 100 patient years (95% CI 173-256). Infections were predominately mild to moderate and consisted mostly of upper respiratory tract infections, herpes zoster and urinary tract infections. The rate of serious infections was approximately 25 per 100 patient years. The most frequently reported serious infection in the Ikgdar IV group was pneumonia at a frequency of 4%.

In GPA/MPA Study 2, 30/57 (53%) patients in the Ikgdar IV arm and 33/58 (57%) in the azathioprine arm reported infections. The incidence of all grade infections was similar between the arms. Infections were predominately mild to moderate. The most common infections in the Ikgdar IV arm included upper respiratory tract infections, gastroenteritis, urinary tract infections and herpes zoster. The incidence of serious infections was similar in both arms (12%). The most commonly reported serious infection in the Ikgdar IV arm was mild or moderate bronchitis.

In the pediatric GPA/MPA study, 91% of the reported infections were non-serious and 90% were mild to moderate. The most common infections in the overall study period were: upper respiratory tract infections (URTIs) (48%), influenza (24%), conjunctivitis (20%), nasopharyngitis (20%), lower respiratory tract infections (16%), sinusitis (16%), viral URTIs (16%), ear infection (12%), gastroenteritis (12%), pharyngitis (12%), urinary tract infection (12%). Serious infections were reported in 7 patients (28%), and included: influenza (2 patients [8%]) and lower respiratory tract infection (2 patients [8%]) as the most frequently reported events.

Malignancies:
In GPA/MPA Study 1, the incidence of malignancy in Ikgdar IV treated patients was 2.05 per 100 patient years. On the basis of standardized incidence ratios, this malignancy rate appears to be similar to rates previously reported in GPA and MPA populations.

In the pediatric GPA/MPA study, no malignancies were reported with a follow-up period of up to 54 months.

Laboratory Abnormalities
Hypogammaglobulinaemia (IgG or IgM below the lower limit of normal) has been observed in pediatric GPA/MPA patients treated with Ikgdar IV. During the overall study period, 3/25 (12%) patients reported an event of hypogammaglobulinaemia, 18 patients (72%) had prolonged (defined as Ig levels below lower limit of normal for at least 4 months) low IgG levels (of whom 15 patients also had prolonged low IgM). Three patients received treatment with intravenous immunoglobulin (IV-IG). There was no

association between prolonged low IgG and IgM and an increased risk of serious infection.

Clinical Trial Experience in Pemphigus Vulgaris

PV Study 1 (Study ML22196)

Summary of the safety profile in PV Study 1

The safety profile of Rituximab in combination with short term, low dose, glucocorticoids in the treatment of patients with pemphigus vulgaris was studied in a randomized, controlled, multicenter, open-label study in 38 pemphigus vulgaris (PV) and 8 pemphigus foliaceus (PF) patients (PV Study 1). Patients randomized to the Rituximab IV group received an initial 1000 mg IV on Study Day 1 and a second 1000 mg IV on Study Day 15. Maintenance doses of 500 mg IV were administered at Months 12 and 18. Patients could receive 1000mg IV at the time of relapse. The safety profile of Rituximab IV in patients with PV was consistent with that observed in RA and GPA/MPA patients.

Adverse drug reactions from PV Study 1 are presented in Table 5 and were adverse events which occurred at a rate of ≥5% among Rituximab IV treated PV patients, with a ≥ 2% absolute difference in incidence between the Rituximab IV treated group and the standard dose prednisone group up to Month 24. No patients were withdrawn due to ADRs. Frequencies in Table 5 are defined as very common (≥1/10) and common (≥1/100).

Table 5 ADRs for Rituximab IV-treated Pemphigus Vulgaris Patients from PV Study 1 (up to Month 24)

Adverse drug reactions			Rituximab IV + low dose prednisone N = 38	Standard dose prednisone N = 36
System Organ Class	**Very Common (≥ 1/10)**	**Common (≥ 1/100)**		
Injury, Poisoning and Procedural Complications	Infusion related reactions*		22 (58%)	N/A
Skin and Subcutaneous Tissue Disorders	Alopecia		5 (13%)	0
		Pruritus	2 (5%)	0
		Urticaria	2 (5%)	0
		Skin disorder	2 (5%)	0
Psychiatric Disorders	Persistent depressive disorder		5 (13%)	3 (8%)
		Major depression	2 (5%)	1 (3%)
		Irritability	2 (5%)	0
Infections and Infestations		Herpes virus infection	3 (8%)	0
		Herpes zoster	2 (5%)	1 (3%)
		Oral herpes	2 (5%)	1 (3%)
		Conjunctivitis	2 (5%)	0
General Disorders and Administration Site Conditions		Fatigue	3 (8%)	2 (6%)
		Pyrexia	2 (5%)	0
Nervous System Disorders		Headache	2 (5%)	1 (3%)
		Dizziness	2 (5%)	0
Gastrointestinal Disorders		Abdominal pain upper	2 (5%)	1 (3%)
Cardiac Disorders		Tachycardia	2 (5%)	0
Musculoskeletal and Connective Tissue Disorders		Musculoskeletal pain	2 (5%)	0
Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)		Skin papilloma	2 (5%)	0

Note:
* Infusion-related reactions included symptoms collected on the next scheduled visit after each infusion, and adverse events occurring on the day of or one day after the infusion. The most common infusion-related reaction symptoms/Preferred Terms included headaches, chills, high blood pressure, nausea, asthenia and pain. Adverse drug reactions were defined as adverse events which occurred at a rate of ≥ 5%, with an absolute ≥ 2% difference in incidence between the Rituximab IV + low dose prednisone group and the standard dose prednisone group. ADRs are listed in descending order of frequency by system organ class.

PV Study 2 (Study WA29330)

Summary of the safety profile in PV Study 2

In PV Study 2, a randomized, double-blind, double-dummy, active-comparator, multicenter study evaluating the efficacy and safety of Rituximab IV compared with mycophenolate mofetil (MMF) in patients with moderate-to-severe active PV requiring oral corticosteroids, 67 PV patients received treatment with Rituximab IV (initial 1000 mg IV on Study Day 1 and a second 1000 mg IV on Study Day 15 repeated at Weeks 24 and 26) for up to 52 weeks.

In PV Study 2, the safety profile of Rituximab IV was consistent with the established safety profile in other approved autoimmune indications. In PV Study 2, ADRs were defined as adverse events occurring in ≥ 5% of patients in the Rituximab IV arm and assessed as related and are presented in Table 6.

Table 6 ADRs for Rituximab IV-treated Pemphigus Vulgaris Patients (N=67) from PV Study 2 (up to Week 52).

System Organ Class	Very Common (≥ 1/10)	Common (≥ 1/100)	Ikgdar IV (N=67)
Injury, Poisoning and Procedural Complications	Infusion related reaction*		15 (22%)
Nervous System disorders	Headache		10 (15%)
		Dizziness	4 (6)%
Infections and Infestations	Upper respiratory tract infection		7 (10%)
		Nasopharyngitis	6 (9%)
		Oral candidiasis	6 (9%)
		Urinary tract infection	5 (8%)
Musculoskeletal and connective tissue disorders		Arthralgia	6 (9%)
		Back pain	6 (9%)
General Disorders and Administration Site Conditions		Fatigue	5 (8%)
		Asthenia	4 (6%),

* The most common infusion-related reaction symptoms/Preferred Terms for PV Study 2 were dyspnoea, erythema, hyperhidrosis, flushing/hot flush, hypotension/low blood pressure and rash/rash pruritic.

Further information on selected adverse drug reactions:

Infusion-related reactions

In PV Study 1, infusion-related reactions were retrospectively collected and assessed, and included symptoms of intolerance or adverse events considered to be infusion-related. Infusion-related reactions were reported very commonly (58%). All infusion-related reactions were mild to moderate (Grade 1 or 2) except one Grade 3 serious infusion-related reaction (arthralgia) associated with the Month 12 maintenance infusion. The proportion of patients experiencing an infusion- related reaction was 29% (11 patients), 40% (15 patients), 13% (5 patients), and 10% (4 patients) following the first, second, third, and fourth infusions, respectively. There were no fatal infusion-related reactions and no patients were withdrawn from treatment due to infusion-related reactions. Symptoms of infusion-related reactions were similar in type and severity to those seen in RA and GPA/MPA patients.

In PV Study 2, IRRs occurred primarily at the first infusion and the frequency of IRRs decreased with subsequent infusions: 17.9%, 4.5%, 3% and 3% of patients experienced

IRRs at the first, second, third, and fourth infusions, respectively. In 11/15 patients who experienced at least one IRR, the IRRs were Grade 1 or 2. In 4/15 patients, Grade ≥3 IRRs were reported and led to discontinuation of Ikgdar treatment; three of the four patients experienced serious [life-threatening] IRRs. Serious IRRs occurred at the first (2 patients) or second (1 patient) infusion and resolved with symptomatic treatment

Infections

In PV Study 1, 14 patients (37%) in the Rituximab IV group experienced treatment-related infections compared to 15 patients (42%) in the standard dose prednisone group. The most common infections in the Rituximab IV group were herpes simplex and zoster infections, bronchitis, urinary tract infection, fungal infection, and conjunctivitis. Three patients (8%) in the Rituximab IV group experienced a total of 5 serious infections (Pneumocystis jirovecii pneumonia, infective thrombosis, intervertebral discitis, lung infection, Staphylococcal sepsis) and one patient (3%) in the standard dose prednisone group experienced a serious infection (Pneumocystis jirovecii pneumonia)

In PV Study 2, 42 patients (62.7%) in the Rituximab IV arm experienced infections. The most common infections in the Rituximab IV group were upper respiratory tract infection, nasopharyngitis, oral candidiasis and urinary tract infection. Six patients (9%) in the Rituximab IV arm experienced serious infections.

Laboratory Abnormalities

Intravenous Formulation

Hypogammaglobulinaemia (IgG or IgM below the lower limit of normal) has been observed in RA and adult and pediatric GPA/MPA patients treated with Ikgdar IV. There was no increased rate in overall infections or serious infections after the development of low IgG or IgM. In PV Study 2, low IgG levels were commonly observed and low IgM levels were very commonly observed, however, there was no evidence of an increased risk of serious infections after the development of low IgG or IgM.

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

In placebo-controlled periods of clinical trials, 0.94% (13/1382) of Ikgdar IV treated patients and 0.27% (2/731) of placebo patients developed severe (Grade 3 or 4) neutropenia. In these studies, rates of severe neutropenia were 1.06 and 0.53 per 100 patient years, respectively after the first treatment course, and 0.97 and 0.88 per 100 patient years, respectively after multiple courses. Therefore, neutropenia can be considered an ADR for the first course only. Time to onset of neutropenia was variable. In clinical trials neutropenia was not associated with an observed increase in serious

infection and most patients continued to receive additional courses of Ikgdar IV after episodes of neutropenia.

Adult patients with Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA) Patients

In the induction of remission clinical trial, at 6 months, in the Ikgdar IV group, 27%, 58% and 51% of patients with normal immunoglobulin levels at baseline had low IgA, IgG and IgM levels, respectively compared to 25%, 50% and 46%, respectively in the cyclophosphamide group.

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

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

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

Pemphigus Vulgaris

In PV Study 2, in the Rituximab IV arm, transient decreases in lymphocyte count, driven by decreases in the peripheral T-cell populations, as well as a transient decrease in phosphorus level were very commonly observed post-infusion. These were considered to be induced by IV methylprednisolone premedication infusion.

2.6.2 Post Marketing Experience

Intravenous Formulation

Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukaemia Patients

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

Additional cases of severe IRRs have been reported during post-marketing use of Ikgdar IV *(see section 2.4 Warnings and Precautions)*.

As part of the continuing post-marketing surveillance of Ikgdar IV safety, the following serious adverse reactions have been observed:

<u>*Cardiovascular system*</u>:

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

Respiratory system:

Respiratory failure/insufficiency and lung infiltration in the context of IRRs have been observed *(see section 2.4 Warnings and Precautions)*. In addition to pulmonary events associated with infusions, interstitial lung disease, some with fatal outcome, has been reported.

Blood and lymphatic system:

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

Skin and appendages:

Severe bullous skin reactions including fatal cases of toxic epidermal necrolysis and Stevens-Johnson syndrome have been reported rarely.

Nervous system:

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

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

Body as a whole:

Serum sickness-like reactions have been reported rarely.

Infections and infestations:

Cases of hepatitis B reactivation have been reported, the majority of which were in subjects receiving Ikgdar IV in combination with cytotoxic chemotherapy *(see section 2.4 Warnings and Precautions for Use)*.

Other serious viral infections, either new, reactivation or exacerbation, some of which were fatal, have been reported with Ikgdar IV treatment. The majority of patients had received Ikgdar IV 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 (CMV), Varicella zoster virus and Herpes simplex virus)*, JC virus (*progressive multifocal leukoencephalopathy (PML)) see section 2.4 Warnings and Precautions*) and Hepatitis C virus.

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

Gastro-intestinal system:

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

Rheumatoid Arthritis (RA), Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA) Patients

As part of the continuing post-marketing surveillance of Ikgdar IV safety, the following have been observed in the RA setting and are also expected, if not already observed, in GPA/MPA patients:

Infections and Infestations:
Progressive multifocal leukoencephalopathy (PML) and reactivation of hepatitis B infection have been reported.

Body as a whole:
Serum sickness-like reaction has been reported.

Skin and subcutaneous tissue disorders:
Toxic epidermal necrolysis and Stevens-Johnson syndrome some with fatal outcome have been reported very rarely.

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

Nervous system:
Cases of posterior reversible encephalopathy syndrome (PRES) / reversible posterior

leukoencephalopathy syndrome (RPLS) have been reported. Signs and symptoms include visual disturbance, headache, seizures and altered mental status, with or without associated hypertension. A diagnosis of PRES/RPLS requires confirmation by brain imaging. The reported cases had recognized risk factors for PRES/RPLS, including hypertension, immunosuppressive therapy and/or other concomitant therapies

General disorders and administration site conditions:
Severe IRRs some with fatal outcome have been reported (see *section 2.6 Undesirable Effects, Clinical Trials*)
Laboratory Abnormalities

Intravenous Formulation

Non-Hodgkin's Lymphoma

Blood and lymphatic system:

Rarely the onset of neutropenia has occurred more than four weeks after the last infusion of Ikgdar IV**.**

In studies of Ikgdar IV in patients with Waldenstrom's macroglobulinemia, 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.

2.7 Overdose

Intravenous Formulations

Limited experience with doses higher than the approved intravenous doses of Ikgdar IV is available from clinical trials in humans. The highest IV dose tested in humans to date is 5000 mg (2250 mg/m^2), tested in a dose escalation study in patients with chronic lymphocytic leukaemia No additional safety signals were identified. Patients who experience overdose should have immediate interruption of their infusion and be closely monitored.

Consideration should be given to the need for regular monitoring of blood cell count and for increased risk of infections while patients are B cell-depleted.

2.8 Interactions with other medicinal products and other forms of interaction

At present, there are limited data on possible drug interactions with Ikgdar.

In CLL patients, co-administration with Ikgdar IV 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 Ikgdar.

Co-administration with methotrexate had no effect on the pharmacokinetics of Ikgdar IV in RA patients.

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

In the RA clinical trial program, 373 Ikgdar IV-treated patients received subsequent therapy with other disease-modifying antirheumatic drugs (DMARDs), of whom 240 received a biologic DMARD. In these patients the rate of serious infection while on Ikgdar IV (prior to receiving a biologic DMARD) was 6.1 per 100 patient years compared to 4.9 per 100 patient years following subsequent treatment with the biologic DMARD

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 Pharmacodynamic Properties

3.1.1 Mechanism of Action

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

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

Peripheral B-cell counts declined to levels below normal following the first dose of Ikgdar. In patients treated for hematological malignancies, B cell recovery began within 6 months of treatment and generally returning to normal levels within 12 months after completion of therapy, although in some patients this may take longer (*see section 2.6 Undesirable Effects, Clinical Trials, Experience from Clinical Trials in Haemato-Oncology*).

In patients with rheumatoid arthritis, the duration of peripheral B cell depletion was variable. The majority of patients received further treatment prior to full B cell repletion.

A small proportion of patients had prolonged peripheral B-cell depletion lasting 2 years or more after their last dose of Ikgdar IV.

In GPA and MPA patients, peripheral blood CD19 B-cells depleted to less than 10 cells/µl following the first two infusions of rituximab and remained at that level in most patients through month 6.

Of 67 patients evaluated for human anti-mouse antibody (HAMA), none were positive. Of 356 non-Hodgkin's lymphoma patients evaluated for human anti-chimeric antibody (HACA) 1.1% (4 patients) were positive.

3.1.2 Clinical / Efficacy Studies

Intravenous Formulation

Low-grade or follicular non-Hodgkin's lymphoma

Ikgdar IV Monotherapy

Initial treatment, weekly for 4 doses

In the pivotal study, 166 patients with relapsed or chemoresistant low-grade or follicular B-cell NHL received 375 mg/m^2 of Ikgdar as an. IV infusion weekly for four doses. The overall response rate (ORR) in the intent-to-treat (ITT) population was 48% ($CI_{95\%}$ 41% – 56%) with a 6% complete response (CR) and a 42% partial response (PR) rate. The projected median time to progression (TTP) for responding patients was 13.0 months.

In a subgroup analysis, the ORR was higher in patients with IWF B, C, and D histologic subtypes as compared to IWF A subtype (58% vs 12%), higher in patients whose largest lesion was <5 cm vs >7 cm in greatest diameter (53% vs 38%), and higher in patients with chemosensitive relapse as compared to chemoresistant (defined as duration of response <3 months) relapse (50% vs 22%). ORR in patients previously treated with autologous bone marrow transplant (ABMT) was 78% versus 43% in patients with no ABMT. Neither age, sex, lymphoma grade, initial diagnosis, presence or absence of bulky disease, normal or high LDH nor presence of extranodal disease had a statistically significant effect (Fisher's exact test) on response to Ikgdar IV.

A statistically significant correlation was noted between response rates and bone marrow involvement. Forty percent of patients with bone marrow involvement responded compared to 59% of patients with no bone marrow involvement (p=0.0186). This finding was not supported by a stepwise logistic regression analysis in which the following factors were identified as prognostic factors: histologic type, bcl-2 positivity at baseline, resistance to last chemotherapy and bulky disease.

Initial treatment, weekly for 8 doses

In a multi-center, single-arm study, 37 patients with relapsed or chemoresistant, low grade or follicular B-cell NHL received 375 mg/m^2 of Ikgdar as IV infusion weekly for eight doses. The ORR was 57% ($CI_{95\%}$ 41% – 73%; CR 14%, PR 43%) with a projected median TTP for responding patients of 19.4 months (range 5.3 to 38.9 months).

Initial treatment, bulky disease, weekly for 4 doses

In pooled data from three studies, 39 patients with relapsed or chemoresistant, bulky disease (single lesion ≥10 cm in diameter), low grade or follicular B-cell NHL received 375 mg/m^2 of Ikgdar as i.v. infusion weekly for four doses. The ORR was 36% ($CI_{95\%}$ 21% – 51%; CR 3%, PR 33%) with a median TTP for responding patients of 9.6 months (range 4.5 to 26.8 months).

Re-treatment, weekly for 4 doses

In a multi-center, single-arm study, 58 patients with relapsed or chemoresistant low grade or follicular B-cell NHL, who had achieved an objective clinical response to a prior course of Ikgdar, were re-treated with 375 mg/m^2 of Ikgdar as i.v. infusion weekly for four doses. Three of the patients had received two courses of Ikgdar before enrollment and thus were given a third course in the study. Two patients were re-treated twice in the study. For the 60 re-treatments on study, the ORR was 38% ($CI_{95\%}$ 26% – 51%; 10% CR, 28% PR) with a projected median TTP for responding patients of 17.8 months (range 5.4 – 26.6). This compares favorably with the TTP achieved after the prior course of Ikgdar IV (12.4 months).

Ikgdar IV In combination with chemotherapy

Initial treatment

In an open-label randomized trial, a total of 322 previously untreated patients with follicular lymphoma were randomized to receive either CVP chemotherapy (cyclophosphamide 750 mg/m^2, vincristine 1.4 mg/m^2 up to a maximum of 2 mg on day 1, and prednisolone 40 mg/m^2/day on days 1-5) every 3 weeks for 8 cycles or Ikgdar IV 375 mg/m^2 in combination with CVP (R-CVP). Ikgdar IV was administered on the first day of each treatment cycle. A total of 321 patients (162 R-CVP, 159 CVP) received therapy and were analyzed for efficacy.

The median follow-up of patients was 53 months. R-CVP led to a significant benefit over CVP for the primary endpoint, time to treatment failure (27 months vs. 6.6 months, $p < 0.0001$, log-rank test). The proportion of patients with a tumor response (CR, CRu, PR) was significantly higher ($p< 0.0001$ Chi-Square test) in the R-CVP group (80.9%) than the CVP group (57.2%). Treatment with R-CVP significantly prolonged the time to disease progression or death compared to CVP, 33.6 months and 14.7 months, respectively ($p < 0.0001$, log-rank test). The median duration of response was 37.7 months in the R-CVP group and was 13.5 months in the CVP group ($p < 0.0001$, log-rank test). The difference between the treatment groups with respect to overall survival showed a strong clinical benefit (p=0.029, log-rank test stratified by center): survival

rates at 53 months were 80.9% for patients in the R-CVP group compared to 71.1% for patients in the CVP group.

Results from three other randomized trials using Ikgdar IV in combination with chemotherapy regimen other than 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 four studies are summarized in the table 7 below.

Table 7 Summary of key results from four phase III randomized studies evaluating the benefit of Ikgdar IV 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

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

Ikgdar IV Maintenance therapy

Previously untreated follicular NHL

In a prospective, open label, international, multi-center, phase III trial 1193 patients with previously untreated advanced follicular lymphoma received induction therapy with R-CHOP (n=881), R-CVP (n=268) or R-FCM (n=44), according to the investigators' choice. A total of 1078 patients responded to induction therapy, of which 1018 were randomized to Ikgdar IV maintenance therapy (n=505) or observation (n=513). The two treatment groups were well balanced with regards to baseline characteristics and disease status. Ikgdar IV maintenance treatment consisted of a single infusion of Ikgdar IV at 375 mg/m^2 BSA given every 2 months until disease progression or for a maximum period of two years.

The pre-specified primary analysis was conducted at a median observation time of 25 months from randomization, maintenance therapy with Ikgdar IV resulted in a clinically relevant and statistically significant improvement in the primary endpoint of investigator assessed progression-free survival (PFS) as compared to observation in patients with previously untreated follicular NHL. This improvement in PFS was confirmed by an independent review committee (IRC) (see Table 8 below).

Significant benefit from maintenance treatment with Ikgdar IV was also seen for the secondary endpoints event-free survival (EFS), time to next anti-lymphoma treatment (TNLT) time to next chemotherapy (TNCT) and overall response rate (ORR) (see Table 8 below).

Data from extended follow-up of patients in the study (median follow-up 9 years) confirmed the long-term benefit of Ikgdar IV maintenance therapy in terms of PFS, EFS, TNLT and TNCT (See Table 8 below)

Table 8 Overview of Efficacy Results for Maintenance Ikgdar IV vs. Observation (25 Months and 9 Years Median Follow-up - Final Analysis)

	Primary analysis (median FU: 25 months)		Final analysis (median FU: 9.0 years)	
	Observation N=513	**Ikgdar N=505**	**Observation N=513**	**Ikgdar N=505**
Primary efficacy				
Progression-free survival (median)	NR	NR	4.06 years	10.49 years
log-rank p value	<0.0001		<0.0001	
hazard ratio (95% CI)	0.50 (0.39, 0.64)		0.61 (0.52, 0.73)	
risk reduction	50%		39%	
Secondary efficacy				
Overall survival (median)	NR	NR	NR	NR
log-rank p value	0.7246		0.7953	
hazard ratio (95% CI)	0.89 (0.45, 1.74)		1.04 (0.77, 1.40)	
risk reduction	11%		-6%	
Event-free survival (median)	38 months	NR	4.04 years	9.25 years
log-rank p value	<0.0001		<0.0001	
hazard ratio (95% CI)	0.54 (0.43, 0.69)		0.64 (0.54, 0.76)	
risk reduction	46%		36%	
TNLT (median)	NR	NR	6.11 years	NR
log-rank p value	0.0003		<0.0001	
hazard ratio (95% CI)	0.61 (0.46, 0.80)		0.66 (0.55, 0.78)	
risk reduction	39%		34%	
TNCT (median)	NR	NR	9.32 years	NR
log-rank p value	0.0011		0.0004	
hazard ratio (95% CI)	0.60 (0.44, 0.82)		0.71 (0.59, 0.86)	
risk reduction	40%		39%	
Overall response rate*	55%	74%	61%	79%
chi-squared test p value	<0.0001		<0.0001	
odds ratio (95% CI)	2.33 (1.73, 3.15)		2.43 (1.84, 3.22)	
Complete response (CR/CRu) rate*	48%	67%	53%	67%
chi-squared test p value	<0.0001		<0.0001	
odds ratio (95% CI)	2.21 (1.65, 2.94)		2.34 (1.80, 3.03)	

* at end of maintenance/observation; final analysis results based on median follow-up of 73 months.
FU: follow-up; NR: not reached at time of clinical cut off, TNCT: time to next chemotherapy treatment; TNLT: time to next anti lymphoma treatment.

Ikgdar IV maintenance treatment provided consistent benefit in all subgroups tested: gender (male, female), age (<60 years, >= 60 years), FLIPI score (1, 2 or 3), induction

therapy (R-CHOP, R-CVP or R-FCM) and regardless of the quality of response to induction treatment (CR or PR).

Relapsed/Refractory follicular NHL

In a prospective, open label, international, multi-centre, phase III trial, 465 patients with relapsed/refractory follicular NHL were randomised in a first step to induction therapy with either CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone; n=231) or Ikgdar IV plus CHOP (R-CHOP, n=234). The two treatment groups were well balanced with regard to baseline characteristics and disease status. A total of 334 patients achieving a complete or partial remission following induction therapy were randomised in a second step to Ikgdar IV maintenance therapy (n=167) or observation (n=167). Ikgdar IV maintenance treatment consisted of a single infusion of Ikgdar IV at 375 mg/m^2 BSA given every 3 months until disease progression or for a maximum period of two years.

The final efficacy analysis included all patients randomized to both parts of the study. After a median observation time of 31 months for patients randomised to the induction phase, R-CHOP significantly improved the outcome of patients with relapsed/refractory follicular NHL when compared to CHOP (see Table 9).

Table 9 – Induction phase: overview of efficacy results for CHOP vs R-CHOP (31 months median observation time)

	CHOP	R-CHOP	p-value	Risk Reduction[1)]
Primary Efficacy				
ORR[2)]	74%	87%	0.0003	NA
CR[2)]	16%	29%	0.0005	NA
PR[2)]	58%	58%	0.9449	NA
Secondary Efficacy				
OS (median)	NR	NR	0.0508	32%
PFS(median)	19.4 mo.	33.2 mo.	0.0001	38%

[1)] Estimates were calculated by hazard ratios

[2)] Last tumor response as assessed by the investigator. The "primary" statistical test for "response" was the trend test of CR versus PR versus non-response ($p < 0.0001$)

Abbreviations: NA, not available; NR, not reached; mo, months; ORR: overall response rate; CR: complete response; PR: partial response; OS: overall survival: PFS: progression free survival

For patients randomized to the maintenance phase of the trial, the median observation time was 28 months from maintenance randomisation. Maintenance treatment with Ikgdar IV led to a clinically relevant and statistically significant improvement in the primary endpoint, PFS, *(time from maintenance randomisation to relapse, disease progression or death)* when compared to observation alone ($p<0.0001$ log-rank test). The median PFS was 42.2 months in the Ikgdar IV maintenance arm compared to 14.3 months in the observation arm. Using a cox regression analysis, the risk of experiencing progressive disease or death was reduced by 61% with Ikgdar IV maintenance treatment

when compared to observation (95% CI; 45%-72%). Kaplan-Meier estimated progression-free rates at 12 months were 78% in the Ikgdar IV maintenance group vs 57% in the observation group. An analysis of overall survival confirmed the significant benefit of Ikgdar IV maintenance over observation (p=0.0039 log-rank test). Ikgdar IV maintenance treatment reduced the risk of death by 56% (95% CI; 22%-75%).

The median time to new anti-lymphoma treatment was significantly longer with Ikgdar IV maintenance treatment than with observation (38.8 months vs. 20.1 months, p<0.0001 log-rank test). The risk of starting a new treatment was reduced by 50% (95% CI; 30%-64%). In patients achieving a CR/CRu (complete response unconfirmed) as best response during induction treatment, Ikgdar IV maintenance treatment significantly prolonged the median disease free survival (DFS) compared to the observation group (53.7 vs 16.5 months, p=0.0003 log-rank test) (see table 10 below). The risk of relapse in complete responders was reduced by 67% (95% CI; 39%-82%).

Table 10 – Maintenance phase: overview of efficacy results Ikgdar IV vs. observation (28 months median observation time)

Efficacy Parameter	**Kaplan-Meier Estimate of Median Time to Event (Months)**			**Risk Reduction**
	Observation (N = 167)	**Ikgdar (N=167)**	**Log-Rank p value**	
Progression-free survival (PFS)	14.3	42.2	<0.0001	61%
Overall Survival	NR	NR	0.0039	56%
Time to new lymphoma treatment	20.1	38.8	<0.0001	50%
Disease-free survival[a]	16.5	53.7	0.0003	67%
Subgroup Analysis				
PFS				
CHOP	11.6	37.5	<0.0001	71%
R-CHOP	22.1	51.9	0.0071	46%
CR	14.3	52.8	0.0008	64%
PR	14.3	37.8	<0.0001	54%
OS				
CHOP	NR	NR	0.0348	55%
R-CHOP	NR	NR	0.0482	56%

NR: not reached; [a]: only applicable to patients achieving a CR

The benefit of Ikgdar IV maintenance treatment was confirmed in all subgroups analysed, regardless of induction regimen (CHOP or R-CHOP) or quality of response to induction treatment (CR or PR) (see table 10). Ikgdar IV maintenance treatment significantly prolonged median PFS in patients responding to CHOP induction therapy (median PFS 37.5 months vs 11.6 months, p<0.0001) as well as in those responding to R-CHOP induction (median PFS 51.9 months vs 22.1 months, p=0.0071). Ikgdar maintenance treatment also provided a clinically meaningful benefit in terms of overall survival for both patients responding to CHOP and patients responding to R-CHOP in the induction phase of the study.

Ikgdar maintenance treatment provided consistent benefit in all subgroups tested gender, age (≤60 years, > 60 years), stage (III, IV), WHO performance status (0 versus >0), B symptoms (absent, present), bone marrow involvement (no versus yes), IPI (0-2 versus 3-5), FLIPI score (0-1, versus 2 versus 3-5), number of extra-nodal sites (0-1 versus >1), number of nodal sites (< 5 versus ≥ 5), number of previous regimens (1 versus 2), best response to prior therapy (CR/PR versus NC/PD), hemoglobin (< 12 g/dL versus ≥12 g/dL), β_2-microglobulin (< 3mg/L versus ≥3 mg/L), LDH (elevated, not elevated) except for the small subgroup of patients with bulky disease.

Adult Diffuse large B-cell non-Hodgkin's lymphoma

In a randomized, open-label trial, a total of 399 previously untreated elderly patients (age 60 to 80 years) with diffuse large B-cell lymphoma received standard CHOP chemo-therapy (cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2 up to a maximum of 2 mg on day 1, and prednisolone 40 mg/m^2/day on days 1 - 5) every 3 weeks for eight cycles, or Ikgdar IV 375 mg/m^2 plus CHOP (R-CHOP). Ikgdar IV was administered on the first day of the treatment cycle.

The final efficacy analysis included all randomized patients (197 CHOP, 202 R-CHOP), and had a median follow-up duration of approximately 31 months. The two treatment groups were well balanced in baseline characteristics and disease status. The final analysis confirmed that R-CHOP significantly increased the duration of event-free survival *(the primary efficacy parameter, where events were death, relapse or progression of lymphoma, or institution of a new anti-lymphoma treatment)* (p=0.0001). Kaplan Meier estimates of the median duration of event-free survival were 35 months in the R-CHOP arm compared to 13 months in the CHOP arm, representing a risk reduction of 41%. At 24 months, estimates for overall survival were 68.2% in the R-CHOP arm compared to 57.4% in the CHOP arm. A subsequent analysis of the duration of overall survival, carried out with a median follow-up duration of 60 months, confirmed the benefit of R-CHOP over CHOP treatment (p=0.0071), representing a risk reduction of 32%.

The analysis of all secondary parameters *(response rates, progression-free survival, disease-free survival, duration of response)* verified the treatment effect of R-CHOP compared to CHOP. The complete response rate after cycle 8 was 76.2% in the R-CHOP group and 62.4% in the CHOP group (p=0.0028). The risk of disease progression was reduced by 46% and the risk of relapse by 51%.

In all patient subgroups *(gender, age, age-adjusted IPI, Ann Arbor stage, ECOG, Beta 2 Microglobulin, LDH, Albumin, B-symptoms, Bulky disease, extranodal sites, bone marrow involvement)*, the risk ratios for event-free survival and overall survival (R-CHOP compared with CHOP) were less than 0.83 and 0.95; respectively. R-CHOP was associated with improvements in outcome for both high- and low-risk patients according to age-adjusted IPI.

Previously untreated and relapsed/ refractory chronic lymphocytic leukaemia

In two open-label randomized trials, a total of 817 previously untreated patients and 552 patients with refractory / relapsed CLL were randomized to receive either FC chemotherapy (fludarabine 25mg/m^2, cyclophosphamide 250 mg/m^2, days 1-3) every 4 weeks for 6 cycles or Ikgdar IV in combination with FC (R-FC). Ikgdar IV was administered at a dosage of 375 mg/m^2 during the first cycle one day prior to chemotherapy and at a dosage of 500 mg/m^2 on day 1 of each subsequent treatment cycle. A total of 810 patients (403 R-FC, 407 FC) the first line study [see Table 11 and table 12 below] and 552 patients (276 R-FC, 276 FC) for the relapsed/refractory study [see Table 13] were analyzed for efficacy.

In the first line study, after a median observation time of 20.7 months, the median progression-free survival (primary endpoint) was 40 months in the R-FC group and 32 months in the FC group ($p < 0.0001$, log-rank test) (see below table 11).The analysis of overall survival showed an improved survival in favor of the R-FC arm (p=0.0427, log-rank test). These results were confirmed with longer follow-up: after a median observation time of 48.1 months, the median PFS was 55 months in the R-FC group and 33 months in the FC group ($p<0.0001$, log-rank test) and overall survival analyses continued to show a significant benefit of R-FC treatment over FC chemotherapy alone (p=0.0319, log-rank test) The benefit in terms of PFS was consistently observed in most patient subgroups analyzed according to disease risk at baseline. (i.e., Binet stages A-C) and was confirmed with longer follow-up (see Table 12)

Table 11 First-line treatment of chronic lymphocytic leukaemia - overview of efficacy results for Ikgdar IV plus FC vs. FC alone (20.7 months median observation time)

Efficacy Parameter	Kaplan-Meier Estimate of Median Time to Event (Months)			Hazard ratio
	FC (N = 407)	R-FC (N=403)	Log-Rank p value	
Progression-free survival (PFS)	32.2 (32.8)***	39.8 (55.3)***	<0.0001 (<0.0001)***	(0.55)***
Overall Survival	NR (NR)***	NR (NR)***	0.0427 (0.0319)***	0.64 (0.73)***
Event Free Survival	31.1 (31.3)***	39.8 (51.8)***	<0.0001 (<0.0001)***	0.55 (0.56)***
Response rate (CR, nPR, or PR)	72.7%	86.1%	<0.0001	n.a.
CR rates	17.2%	36.0%	<0.0001	n.a.
Duration of response*	34.7 (36.2)***	40.2 (57.3)***	0.0040 (<0.0001)***	0.61 (0.56)***
Disease free survival (DFS)**	NR (48.9)***	NR (60.3)***	0.7882 (0.0520)***	0.93 (0.69)***
Time to new CLL treatment	NR (47.2)***	NR (69.7)***	0.0052 (<0.0001)***	0.65 (0.58)***

Response rate and CR rates analysed using Chi-squared Test.
***Values in parentheses correspond to 48.1 months median observation time (ITT population: 409 FC, 408 R-FC).
NR: not reached n.a: not applicable
*: only applicable to patients with CR, nPR or PR as end-of-treatment response;
NR: not reached n.a. not applicable
**: only applicable to patients with CR as end-of-treatment response;

Table 12 Hazard Ratios of Progression-Free Survival According to Binet Stage (ITT) (20.7 Months Median Observation Time)

Progression-free survival (PFS)	Number of patients		Hazard Ratio (95% CI)	Log-Rank p value
	FC	R-FC		
Binet Stage A	22 (22)*	18 (18)*	0.13 (0.03; 0.61) (0.39 (0.15; 0.98))*	0.0025 (0.0370)*
Binet Stage B	257 (259)*	259 (263)*	0.45 (0.32; 0.63) (0.52 (0.41; 0.66))*	<0.0001 (<0.0001)*
Binet Stage C	126 (126)*	125 (126)*	0.88 (0.58; 1.33) (0.68 (0.49; 0.95))*	0.5341 (0.0215)*

CI: Confidence Interval

**Values correspond to 48.1 months median observation time (ITT population: 409 FC, 408 R-FC)*

In the relapsed/refractory study, the median progression-free survival (primary endpoint) was 30.6 months in the R-FC group and 20.6 months in the FC group (p=0.0002, log-rank test). The benefit in terms of PFS was observed in almost all patient subgroups analyzed according to disease risk at baseline. A slight but not significant improvement in overall survival was reported in the R-FC compared to the FC arm.

Table 13 Treatment of relapsed/refractory chronic lymphocytic leukaemia - overview of efficacy results for Ikgdar IV 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 = 276)	R-FC (N=276)	Log-Rank p value	
Progression-free survival (PFS)	20.6	30.6	0.0002	35%
Overall Survival	51.9	NR	0.2874	17%
Event Free Survival	19.3	28.7	0.0002	36%
Response rate (CR, nPR, or PR)	58.0%	69.9%	0.0034	n.a.
CR rates	13.0%	24.3%	0.0007	n.a.
Duration of response*	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.
NR: not reached n.a. not applicable
* only applicable to patients with CR, nPR or PR as best overall response
**: only applicable to patients with CR as best overall response

Results from other supportive studies using Ikgdar IV in combination with other chemotherapy regimens *(including CHOP, FCM, PC, PCM, bendamustine and cladribine)* for the treatment of CLL patients have also demonstrated high overall response rates with promising PFS rates without adding relevant toxicity to the treatment.

Intravenous Formulation

Rheumatoid arthritis

The efficacy and safety of Ikgdar IV rheumatoid arthritis has been demonstrated in a three pivotal, phase III, randomized, placebo-controlled, double-blind, multicenter study .

Eligible patients had active rheumatoid arthritis, diagnosed according to the criteria of the American College of Rheumatology (ACR). Ikgdar was administered as two IV infusions separated by an interval of 15 days. Each course was preceded by an IV infusion of 100 mg methylprednisolone. All patients received concomitant oral methotrexate. In addition, in Study WA17042, all patients received concomitant oral glucocorticoids on days 2 to 7 and on days 8 to 14 following the first infusion.

The retreatment criteria differed between the studies using one of two approaches: 'Treatment to Remission' whereby patients were treated no more frequently than every 6 months if not in DAS28 remission (i.e., DAS28-ESR $\geq$2.6) and 'Treatment as Needed' strategy ('Treatment PRN'), based on disease activity and/or return of clinical symptoms (swollen and tender joint counts $\geq$ 8) and treated no sooner than every 16 weeks.

Study WA17042 (REFLEX) included 517 patients that had experienced an inadequate response or intolerance to one or more tumor necrosis factor (TNF) inhibitor therapies (TNF-IR). . The primary endpoint was the proportion of patients who achieved an ACR20 response at week 24. Patients received 2 x 1000 mg Ikgdar IV or placebo. Patients were followed beyond week 24 for long term endpoints, including radiographic assessment at 56 weeks. During this time, patients could receive further courses of Ikgdar IV under an open label extension study protocol. In the open-label protocol patients received further courses based on the 'Treatment PRN' criteria.

Disease Activity Outcomes

In these studies, Ikgdar IV (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 (see Table 14). Across all development studies, the treatment benefit was similar in patients independent of age, gender, body surface area, race, number of prior treatments or disease status. Patients seropositive for disease-related auto-antibodies (RF and/or anti-CCP) demonstrated consistently high efficacy compared to MTX alone across studies. Efficacy in seropositive patients was higher than that observed in seronegative patients in whom efficacy was modest.

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 CRP (mg/dL).

Table 14 Cross-Study Comparison of ACR Responses (ITT Population)

	Timepoint	**ACR Response**	**Placebo+MTX**	***Rituximab+MTX*** *(2 x 1000 mg)*
Study WA17042 **(TNF-IR)**	*Week 24*		N= 201	*N= 298*
		ACR20	36 (18%)	*153 (51%)****
		ACR50	11 (5%)	*80 (27%)****
		ACR70	3 (1%)	*37 (12%)****

*Significant difference from placebo at the primary timepoint: * p ≤ 0.05, **p ≤ 0.001 ***p ≤ 0.0001*

Patients treated with Ikgdar IV had a significantly greater reduction in disease activity score (DAS28) than patients treated with methotrexate alone. A good to moderate EULAR response was achieved by significantly more Ikgdar IV treated patients compared to patients treated with methotrexate alone (see Table 15).

Table 15 Cross-Study Comparison of DAS28-ESR and EULAR Responses (ITT Population)

	Placebo + MTX	**RTX +MTX** *(2 × 1000mg)*
StudyWA17042(TNF-IR)		
Change in DAS28 at Week 24		
n	***n=201***	***n=298***
Mean Change	-0.4	-1.9***
EULAR Response (Week 24)		
n	n=201	n=298
Moderate	20%	50%***
Good	2%	15%***

Significant difference from placebo at the primary timepoint: * p ≤ 0.05, **p ≤ 0.001 ***p ≤ 0.0001

Inhibition of Joint Damage

In Studies WA17042 and WA17047 Structural joint damage was assessed radiographically and expressed as change in modified Total Sharp Score (TSS) and its components, the erosion score and joint space narrowing score.

Study WA17042 conducted in TNF-IR patients receiving Ikgdar IV in combination with methotrexate, demonstrated significantly less radiographic progression at 56 weeks than patients from the methotrexate alone group. A higher proportion of patients receiving the original Ikgdar IV also had no erosive progression over 56 weeks.

Study WA17047 conducted in methotrexate-naïve patients (755 patients with early RA of between 8 weeks to four years duration), assessed the prevention of structural joint damage as its primary objective *(see section 2.4 Warnings and Precautions)*. Patients received placebo, 2 x 500 mg or 2 x 1000 mg Ikgdar IV infusion. From Week 24 patients could receive further courses of Ikgdar IV (or placebo to Week 104) based on the 'Treatment to Remission' criteria. The primary endpoint of change in modified Total Sharp Score (TSS) demonstrated that only treatment with Ikgdar IV at a dose of 2 x 1000 mg in combination with methotrexate significantly reduced the rate of progression of joint damage (PJD) at 52 weeks compared with placebo + methotrexate (see Table 16).

The reduction in PJD was driven mainly by a significant reduction in the change in Erosion Score.

Inhibition of the rate of progressive joint damage was also observed long-term. Radiographic analysis at 2 years in Study WA17042 demonstrated significantly reduced progression of structural joint damage in patients receiving Ikgdar IV (2 x 1000 mg) + methotrexate compared to methotrexate alone as well as a significantly higher proportion of patients with no progression of joint damage over the 2 year period.

Table 16 Radiographic outcomes at 1 year in Studies WA17042 and WA17047 (MITT population)

	Placebo + MTX	**RTX +MTX** 2 × 1000 mg
Study WA17042 (TNF-IR)	(n = 184)	(n = 273)
Mean Change from Baseline:		
Modified Total Sharp score	2.30	1.01*
Erosion Score	1.32	0.60*
Joint Space narrowing score	0.98	0.41**
Proportion of patients with no radiographic change	46%	53% NS
Proportion of patients with no erosive change	52%	60%* NS
Study WA17047 (MTX- naïve)	***n=232***	***n=244***
Mean Change from Baseline:		
Modified Total Sharp score	1.079	0.359**
Erosion Score	0.738	0.233***
Joint Space narrowing score	0.341	0.126
Proportion of patients with no radiographic change	53%	64%*
Proportion of patients with no erosive change	55%	67%*

Radiographic outcomes were assessed at Week 52 in Study WA17047 and Week 56 in Study WA17042
150 patients originally randomized to placebo + MTX in WA17042 received at least one course of RTX + MTX by one year
* p <0 05, ** p < 0.001, *** p < 0.0001, NS Non Significant

Quality of life outcomes

Ikgdar IV treated patients reported an improvement in all patient-reported outcomes (HAQ-DI, FACIT-Fatigue and SF-36 questionnaires). Significant reductions in disability index (HAQ-DI) and fatigue (FACIT-Fatigue) and improvement in the physical health domain of the SF-36 were observed in patients treated with Ikgdar IV compared to patients treated with methotrexate alone.

Table 17 Cross Study Comparison of HAQ-DI and FACIT-Fatigue responses

	Placebo+MTX[1]	**RTX+MTX[1]** *(2 × 1000mg)*
Study WA17042 (TNF-IR)	***n=201***	***n=298***
- *Mean change in HAQ[a] at Week 24*	-0.1	-0.4***
- *% patients with HAQ MCID at Week 24*	20%	51%
- *Mean change in FACIT-Fatigue[b] at Week 24*	-0.5	-9.1***

[a] Health assessment questionnaire (HAQ),[b] Functional assessment of chronic illness therapy (FACIT- Fatigue)
Significant difference from placebo at the primary timepoint: * $p < 0.05$, ** $p < 0.001$ *** $p \leq 0.0001$
(CMH test for categorical change, ANOVA for mean change, note that the unadjusted mean changes are displayed)

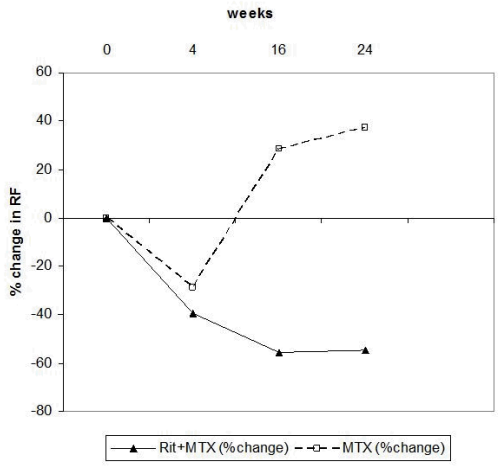
Table 18 Cross-study comparisons of Short Form Health Survey (SF-36).

	Placebo+MTX	**RTX +MTX** *(2 × 1000 mg)*
StudyWA17042(TNF-IR)	***n=197***	***n=294***
Physical Health		
Mean change at Week 24	0.9	5.8***
% patients with MCID at Week 24	13%	48%***
Mental Health		
Mean change at Week 24	1.3	4.7**
% patients with MCID at Week 24	20%	38%**
MCID = minimum clinically important difference defined as an increase of: >6.33 for mental health score and >5.42 for physical health score, % of patients based on number of patients assessable (N) Significant difference from placebo at the primary timepoint: * $p \leq 0.05$, ** $p \leq 0.001$, *** $p \leq 0.0001$ (CMH test for categorical change, ANOVA for mean change - note that unadjusted mean changes are displayed		

Laboratory Evaluations

In rheumatoid factor (RF) positive patients, marked decreases were observed in rheumatoid factor concentrations following treatment with Ikgdar IV in all three studies (range 45-64%, Figure 1)

Figure 1 Percentage Change in Total RF Concentration Over Time in Study 1 (ITT Population, RF-Positive Patients)



Plasma total immunoglobulin concentrations, total lymphocytes counts, and white cell counts generally remained within normal limits following Ikgdar IV treatment, with the exception of a transient drop in white cell counts over the first four weeks following therapy. Titers of IgG antigen specific antibody to mumps, rubella, varicella, tetanus toxoid, influenza and *streptococcus* pneumococci remained stable over 24 weeks following exposure to Ikgdar IV in rheumatoid arthritis patients.

Effects of rituximab on a variety of biomarkers were evaluated in patients enrolled into a clinical study. This sub-study evaluated the impact of a single treatment course of rituximab on levels of biochemical markers, including markers of inflammation (Interleukin 6, C Reactive protein, Serum amyloid type A protein, Protein S100 isotypes A8 and A9), autoantibody (RF and anti-cyclic citrullinated peptide immunoglobulin) production and bone turnover (osteocalcin and procollagen 1 N terminal peptide (P1NP)). Ikgdar IV treatment, whether as monotherapy or in combination with methotrexate or cyclophosphamide reduced the levels of inflammatory markers significantly, relative to methotrexate alone, over the first 24 weeks of follow-up. Levels of markers of bone turnover, osteocalcin and P1NP, increased significantly in the rituximab groups compared to methotrexate alone.

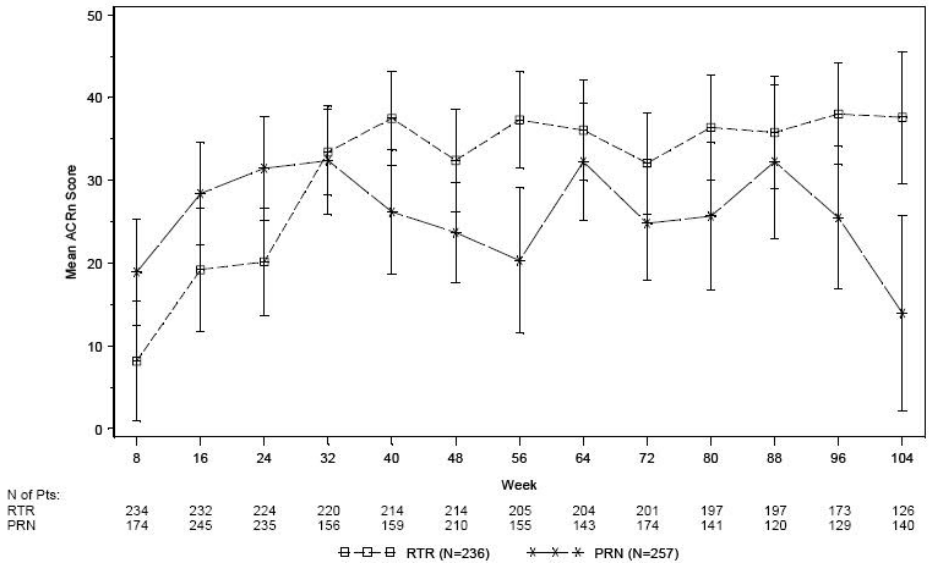
Long-term efficacy with multiple course therapy

In clinical studies patients were retreated based on either a 'Treatment to Remission' or a 'Treatment PRN' strategy. Repeat courses of Ikgdar IV maintained or improved treatment benefit, irrespective of the treatment strategy (*Treatment to Remission or Treatment PRN*) (Figure 2). However, Treatment to Remission generally provided better responses and tighter control of disease activity as indicated by ACRn, DAS28-ESR and HAQ-DI scores over time. Patients treated PRN also experienced returning disease symptoms between courses, as evidenced by DAS28-ESR scores which were close to pre-treatment levels prior to each course (Table 18)

Table 19 Cross-study comparisons of Short Form Health Survey (SF-36).

Population	**Parameter**	**C1**	**C2**	**C3**	**C4**	**C5**
Treatment To Remission		***n=236***	***n=218***	***n=198***	***n=156***	***n=83***
	Mean BL DAS	6.6	4.9	4.6	4.6	4.7
	Median BL ACRn	-	22.7	25.5	26.5	26.3
Treatment PRN		***n=257***	***n=182***	***n=139***	***n=85***	***n=39***
	Mean BL DAS	6.7	6.2	6.2	5.9	6.0
	Median BL ACRn	-	-5.3	-11.1	-10.9	-4.2
Positive change in ACRn = improvement BL=Baseline						

Figure 2 Plot of Mean ACRn Over Time by Treatment Criteria (MTX-IR Population)



Error bars displayed re 95x confidence intervals about the mean No imputation made for mean data RTR = Re-treat to Remission

Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA):

Adult Induction of Remission (GPA/MPA Study 1):

In GPA/MPA Study 1, a total of 197 patients with severe, active, granulomatosis with polyangiitis (Wegener's) (GPA) and MPA were enrolled and treated in an active-controlled, randomized, double-blind, active-controlled multicenter, non-inferiority study Patients were 15 years of age or older, diagnosed with severely, active granulomatosis with polyangiitis (Wegener's) (75% of patients) or microscopic polyangiitis MPA (24% of patients) according to the Chapel Hill Consensus conference criteria. One percent of the patients had unknown GPA and MPA type).

Patients were randomized in a 1:1 ratio to receive either oral cyclophosphamide daily (2mg/kg/day) for 3 to 6 months, followed by azathioprine or Ikgdar IV (375 mg/m2) once weekly for 4 weeks. Patients in both arms received 1000 mg of pulse IV methylprednisolone (or another equivalent-dose glucocorticoid) per day for 1 to 3 days, followed by oral prednisone (1 mg/kg/day, not exceeding 80 mg/day). Prednisone tapering was to be completed by 6 months from the start of study treatment

The primary outcome measure was achievement of complete remission at 6 months defined as a Birmingham Vasculitis Activity Score for Wegener's Granulomatosis BVAS/WG of 0, and off glucocorticoid therapy. The prespecified non-inferiority margin for the treatment difference of 20%. The study demonstrated non-inferiority of Ikgdar IV to cyclophosphamide for complete remission at 6 months. In addition, the complete remission rate in the Ikgdar IV arm was significantly greater than the estimated complete

remission rate in patients with severe GPA and MPA not treated or treated only with glucocorticoids, based on historical control data.

Efficacy was observed both for patients with newly diagnosed GPA and MPA and for patients with relapsing disease.

Table 20 Percentage of Patients Who Achieved Complete Remission at 6 Months (Intent-to-Treat Population)

	Ikgdar (n = 99)	Cyclophosphamide (n = 98)	Treatment Difference (Ikgdar – Cyclophosphamide)
Rate	63.6%	53.1%	10.6%
95.1%[b] CI	(54.1%, 73.2%)	(43.1%, 63.0%)	(-3.2%, 24.3%) [a]

CI = confidence interval.

[a] Non-inferiority was demonstrated since the lower bound (– 3.2%) was higher than the pre-determined noninferiority margin (– 20%).
[b] The 95.1% confidence interval reflects an additional 0.001 alpha to account for an interim efficacy analysis.

Adult Maintenance Treatment (GPA/MPA Study 2):
A total of 117 patients (88 with GPA, 24 with MPA, and 5 with renal-limited ANCA (Associated vasculitis) in disease remission were randomized to receive azathioprine (59 patients) or Ikgdar IV (58 patients) in this prospective, multi-center, controlled, open-label study. Eligible patients were 21 to 75 years of age and had newly diagnosed or relapsing disease in complete remission after combined treatment with glucocorticoids and pulse cyclophosphamide. Patients were ANCA positive at diagnosis or during the course of their disease; had histologically confirmed necrotizing small-vessel vasculitis with a clinical phenotype of GPA/MPA, or renal limited ANCA-associated vasculitis; or both.

Remission-induction therapy included IV prednisone, administered as per the investigator's discretion, preceded in some patients by methylprednisolone pulses, and pulse cyclophosphamide until remission was attained after 4 to 6 months. At that time, and within a maximum of 1 month after the last cyclophosphamide pulse, patients were randomly assigned to receive either Ikgdar IV (two 500 mg IV infusions separated by two weeks (on Day 1 and Day 15) followed by 500 mg IV every 6 months for 18 months or azathioprine (administered orally at a dose of 2 mg/kg/day for 12 months, then 1.5 mg/kg/day for 6 months, and finally 1 mg/kg/day for 4 months (treatment discontinuation after these 22 months). Prednisone treatment was tapered and then kept at a low dose (approximately 5 mg per day) for at least 18 months after randomization. Prednisone dose tapering and the decision to stop prednisone treatment after month 18 were left at the investigator's discretion.

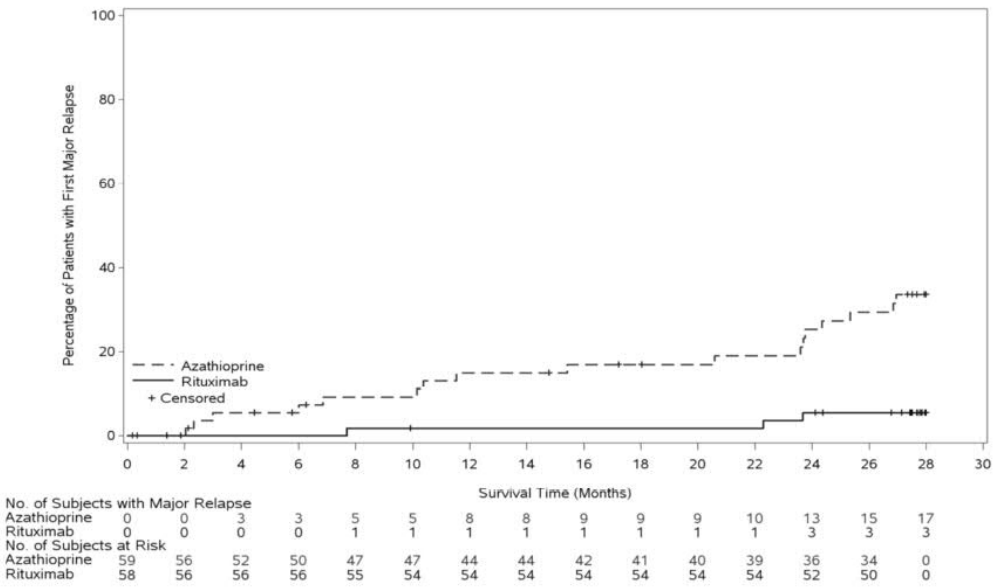
All patients were followed until month 28 (10 or 6 months, respectively, after the last

Ikgdar IV infusion or azathioprine dose). Pneumocystis jirovecii pneumonia prophylaxis was required for all patients with CD4+ T-lymphocyte counts less than 250 per cubic millimeter. The primary outcome measure was the rate of major relapse at month 28.

Results
At month 28, major relapse (defined by the reappearance of clinical and/or laboratory signs of vasculitis activity ([BVAS] > 0) that could lead to organ failure or damage or could be life threatening) occurred in three patients (5%) in the Ikgdar IV group and 17 patients (29%) in the azathioprine group (p=0.0007). Adjusting for the stratification factor using Cox PH modeling, Ikgdar IV reduced the risk of major relapse by approximately 86% relative to azathioprine (hazard ratio [HR]: 0.14; 95% confidence interval [CI]: 0.04, 0.47). Minor relapses (not life threatening and not involving major organ damage) occurred in seven patients in the Ikgdar IV group (12%) and eight patients in the azathioprine group (14%).

The cumulative incidence rate curves showed that time to first major relapse was longer in patients with Ikgdar IV starting from Month 2 and was maintained up to Month 28 (Figure 3)

Figure 3 Cumulative Incidence Over Time of First Major Relapse



Note, patients were censored at Month 28 if they had no event.

3.1.3 IMMUNOGENICITY

As with all therapeutic proteins, there is the potential for an immune response in patients treated with Ikgdar. The data reflects the number of patients whose test results were considered positive for antibodies to rituximab using an enzyme-linked immunosorbent assay (ELISA). Immunogenicity assay results may be influenced by several factors including assay sensitivity and specificity, sample handling, timing of sample collection, concomitant medicinal products and underlying disease. For these reasons, comparison of incidence of antibodies to rituximab with the incidence of antibodies in other studies or to other products may be misleading.

Intravenous Formulation

Rheumatoid Arthritis:

Approximately 10% of patients with rheumatoid arthritis tested positive for anti-drug antibodies (ADA) in the RA clinical studies. The emergence of ADA was not associated with clinical deterioration or with an increased risk of reactions to subsequent infusions in the majority of patients. The presence of ADA may be associated with worsening of infusion or allergic reactions after the second infusion of subsequent courses, and failure to deplete B cells after receipt of further treatment courses has been observed rarely.

Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA)

Twenty-three percent (23/99) of Ikgdar IV-treated patients from the adult GPA and MPA induction of remission trial and 18% (6/34) of Ikgdar IV treated patients in the maintenance therapy clinical trial developed ADA.

There was no apparent trend or negative impact of the presence of ADA on safety or efficacy in the adult GPA and MPA clinical trials.

3.2 Pharmacokinetic Properties

3.2.1 Absorption

Intravenous Formulation

Not applicable.

3.2.2 Distribution

Adult Non-Hodgkin's Lymphoma

Intravenous Formulation

Based on a population pharmacokinetic analysis in 298 NHL patients who received single or multiple infusions of Ikgdar IV as a single agent or in combination with CHOP therapy, 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. The

estimated median terminal elimination half-life of Rituximab was 22 days (range, 6.1 to 52 days). Baseline CD19-positive cell counts and size of measurable tumor lesions contributed to some of the variability in CL_2 of Rituximab in data from 161 patients given 375 mg/m^2 as an i.v. infusion for 4 weekly doses. Patients with higher CD19-positive cell counts or tumor lesions had a higher CL_2. However, a large component of inter-individual variability remained for CL_2 after correction for CD19-positive cell counts and tumor lesion size. V_1 varied by body surface area (BSA) and CHOP therapy. This variability in V_1 (27.1% and 19.0%) contributed by the range in BSA (1.53 to 2.32 m^2) and concurrent CHOP therapy, respectively, were relatively small. Age, gender, race, and WHO performance status had no effect on the pharmacokinetics of Rituximab. This analysis suggests that dose adjustment of Rituximab with any of the tested covariates is not expected to result in a meaningful reduction in its pharmacokinetic variability.

Ikgdar IV at a dose of 375 mg/m^2 was administered as an IV infusion at weekly intervals for 4 doses to 203 patients with NHL naive to Rituximab. The mean C_{max} following the fourth infusion was 486 µg/ml (range, 77.5 to 996.6 µg/ml). The peak and trough serum levels of Rituximab were inversely correlated with baseline values for the number of circulating CD19-positive B-cells and measures of disease burden. Median steady-state serum levels were higher for responders compared with non-responders. Serum levels were higher in patients with International Working Formulation (IWF) subtypes B, C, and D as compared with those with subtype A. Rituximab was detectable in the serum of patients 3 to 6 months after completion of last treatment.

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

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

Chronic Lymphocytic Leukaemia

Intravenous Formulation

Ikgdar IV 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/ m^2 infusion.

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 7.51L). Population pharmacokinetic analysis of the same data gave similar mean values for systemic clearance and half-life, 0.26 L/day and 20.4

days, respectively. Population pharmacokinetic analysis revealed that BSA and gender were the most significant covariates to explain inter-individual variability in pharmacokinetic parameters. After adjusting for BSA, male subjects had a larger volume of distribution and a faster clearance than female subjects. The gender- related pharmacokinetic differences are not considered to be clinically relevant and dose adjustment is not required.

The pharmacokinetics of rituximab were assessed following two IV doses of 500 mg and 1000 mg on Days 1 and 15 in four studies. In all these studies, rituximab pharmacokinetics were dose proportional over the limited dose range studied. Mean C_{max} for serum rituximab following first infusion ranged from 157 to 171 μg/mL for 2 x 500 mg dose and ranged from 298 to 341 μg/mL for 2 x 1000 mg dose. Following second infusion, mean C_{max} ranged from 183 to 198 μg/ml for the 2 × 500 mg dose and ranged from 355 to 404 μg/mL for the 2 × 1000 mg dose. Mean terminal elimination half-life ranged from 15 to 16.5 days for the 2 x 500 mg dose group and 17 to 21 days for the 2 × 1000 mg dose group. Mean C_{max} was 16 to 19% higher following second infusion compared to the first infusion for both doses.

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

The pharmacokinetic parameters in the anti-TNF inadequate responder population, following the same dosage regimen (2 x 1000 mg, IV, 2 weeks apart), were similar with a mean maximum serum concentration of 369 μg/mL and a mean terminal half-life of 19.2 days.

Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA)

The PK parameters in adult with GPA/MPA receiving 375 mg/m^2 Ikgdar IV once weekly for four doses are summarized in Table 21.

Table 21 Population PK adult patients (U2639s/ITN021AI) with GPA/MPA

Parameter	Statistic	Study
		Adult GPA/MPA (U2639s/ITN021AI)
N	Number of Patients	97

Terminal Half-life (days)	Median (Range)	23 (9 to 49)
Clearance (L/day)	Mean (Range)	0.313 (0.116 to 0.726)
Volume of Distribution (L)	Mean (Range)	4.50 (2.25 to 7.39)

The PK parameters of rituximab in adult GPA/MPA patients appear similar to what has been observed in RA patients (*see section 3.2 Pharmacokinetic Properties, Distribution*).

3.2.3 Metabolism

No text.

3.2.4 Elimination

See section 3.2.2 Distribution.

3.2.5 Pharmacokinetics in Special Populations

Renal impairment
No pharmacokinetic data are available in patients with renal impairment.

Hepatic impairment
No pharmacokinetic data are available in patients with hepatic impairment.

3.3 NONCLINICAL SAFETY

3.3.1 Carcinogenicity

No text.

3.3.2 Genotoxicity

No text.

3.3.3 Impairment of Fertility

No text.

3.3.4 Reproductive Toxicity

No text.

4. DESCRIPTION

Rituximab is a genetically engineered chimeric murine/human monoclonal IgG1 kappa antibody directed against the CD20 antigen. Rituximab has an approximate molecular weight of 145 kD. Rituximab is produced by mammalian cell (Chinese Hamster Ovary) suspension culture in a nutrient medium that may contain the antibiotic gentamicin. Gentamicin is not detectable in the final product.

Ikgdar (rituximab) injection is a sterile, preservative-free, clear, colorless solution for intravenous infusion. Ikgdar is supplied at a concentration of 10 mg/mL in either 100 mg/10 mL or 500 mg/50 mL single-dose vials. Each mL of solution contains rituximab, Sodium citrate, polysorbate 80, sodium chloride, sodium hydroxide, hydrochloric acid, water for injections.

5. PATIENT COUNSELLING INFORMATION

Infusion-Related Reactions

Inform patients about the signs and symptoms of infusion-related reactions. Advise patients to contact their healthcare provider immediately to report symptoms of infusion-related reactions including urticaria, hypotension, angioedema, sudden cough, breathing problems, weakness, dizziness, palpitations, or chest pain

Severe Mucocutaneous Reactions

Advise patients to contact their healthcare provider immediately for symptoms of severe mucocutaneous reactions, including painful sores or ulcers on the mouth, blisters, peeling skin, rash, and pustules.

Hepatitis B Virus Reactivation

Advise patients to contact their healthcare provider immediately for symptoms of hepatitis including worsening fatigue or yellow discoloration of skin or eyes.

Progressive Multifocal Leukoencephalopathy (PML)

Advise patients to contact their healthcare provider immediately for signs and symptoms of PML, including new or changes in neurological symptoms such as confusion, dizziness or loss of balance, difficulty talking or walking, decreased strength or weakness on one side of the body, or vision problems.

Tumor Lysis Syndrome (TLS)

Advise patients to contact their healthcare provider immediately for signs and symptoms of tumor lysis syndrome such as nausea, vomiting, diarrhea, and lethargy.

Infections

Advise patients to contact their healthcare provider immediately for signs and symptoms of infections including fever, cold symptoms (e.g., rhinorrhea or laryngitis), flu symptoms (e.g., cough, fatigue, body aches), earache or headache, dysuria, oral herpes simplex infection, and painful wounds with erythema and advise patients of the increased risk of infections during and after treatment with Ikgdar.

Cardiovascular Adverse Reactions

Advise patients of the risk of cardiovascular adverse reactions, including ventricular fibrillation, myocardial infarction, and cardiogenic shock. Advise patients to contact their healthcare provider immediately to report chest pain and irregular heartbeats.

Renal Toxicity

Advise patients of the risk of renal toxicity. Inform patients of the need for healthcare providers to monitor kidney function.

Bowel Obstruction and Perforation

Advise patients to contact their healthcare provider immediately for signs and symptoms of bowel obstruction and perforation, including severe abdominal pain or repeated vomiting.

Embryo-Fetal Toxicity

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy. Advise females of reproductive potential to use effective contraception during treatment with Ikgdar and for at least 12 months after the last dose.

Lactation

Advise women not to breastfeed during treatment with Ikgdar and for at least 6 months after the last dose.

6. PHARMACEUTICAL PARTICULARS

6.1 Storage

Intravenous Formulation

This medicine should not be used after the expiry date (Expiry Date) shown on the pack.

Intravenous Formulation

Store vials at 2°C - 8°C (in a refrigerator). Do not freeze. Keep the container in the outer carton in order to protect from light.

After aseptic dilution in 0.9% aqueous saline solution:

The prepared infusion solution of Ikgdar IV in 0.9% aqueous saline solution is physically and chemically stable for 30 days at 2°C - 8°C plus an additional 24 hours at room temperature.

After aseptic dilution in 5% aqueous dextrose solution:
The prepared infusion solution of Ikgdar IV in 5% aqueous dextrose solution is physically and chemically stable for 24 hours at 2°C - 8°C plus an additional 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.

6.2 Special Instructions for Use, Handling and Disposal

Intravenous Formulation

Use sterile needle and syringe to prepare Ikgdar. Withdraw the required amount of Ikgdar under aseptic conditions and dilute to a calculated rituximab concentration of 1 – 4 mg/mL in an infusion bag containing sterile, non-pyrogenic 0.9%, aqueous saline solution or 5% aqueous dextrose solution. To mix the solution, gently invert the bag 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 medications should be inspected visually for particulate matter or discoloration prior to administration.

The prepared infusion solution of Ikgdar IV is physically and chemically stable for 24 hours at 2°C - 8°C and subsequently 12 hours at room temperature.

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

Intravenous Formulation

Disposal of unused/expired medicines

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established “collection systems”, if available in your location.

The following points should be strictly adhered to regarding the use and disposal of syringes and other medicinal sharps:

- Needles and syringes should never be reused.
- Place all used needles and syringes into a sharps container (puncture-proof disposable container).

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

6.3 Packs

Vial of 10 ml (10 mg/ml)	1
Vial of 50 ml (10 mg/ml)	1

6.4 Shelf life

30 months when stored at recommended storage conditions

Medicine: keep out of reach of children

7. DETAILS OF MANUFACTURER

Manufactured by:
F. Hoffmann-La Roche Ltd., Grenzacherstrasse 124, CH-4070, Basel, Switzerland at
1. Roche Diagnostic GmbH, Sandhofer Strasse, 116, D 68305 Mannheim, Germany.
2. M/s. Genentech Inc., 4625 NE Brookwood Parkway, Hillsboro, OR 97124, USA.

Imported by:
Roche Products (India) Pvt. Ltd.,
C/O. Parekh Integrated Services Pvt Ltd,
Gala No. A1, First Floor, Warehouse no. 6,
BGR Logistics Park, NH-3, Zone 5, Bhiwandi,
Maharashtra (India) – 421302

Distributed and Marketed by:
Cipla Ltd.,
Cipla House, Peninsula Business Park, Ganpatrao Kadam Marg, Lower Parel, Mumbai 400 013, India

8. DETAILS OF PERMISSION OR LICENSE NUMBER WITH DATE

Permission no. (122A) (193), dated 8 October, 2002

9. DATE OF REVISION

Current at January 2021, Version 12.0